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ABSTRACT

This report provides expert opinion on the problems of fetal alcohol syndrome (FAS) and ways to inform the public of teratogenic risk of alcohol consumption during pregnancy. In the absence of firm evidence that moderate drinking of alcoholic beverages leads to FAS and uncertainty concerning the effectiveness of labeling of alcoholic beverages, a decision on these problems was made by the Department of the Treasury, Bureau of Alcohol, Tobacco and Firearms. It was decided that the Bureau would work with appropriate federal agencies, with members of all segments of the alcoholic beverage industry, and with other interested groups to develop and implement a program of public education rather than require product labeling at this time. The report includes summaries of experts' comments and an outline of the plan of action to educate the public. Addenda to the report include a review of scientific findings related to alcohol ingestion and fetal outcomes, plus the full texts of the experts' reports. Extensive references to the related literature are included. (Author/RH)

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THE FETAL ALCOHOL SYNDROME
PUBLIC AWARENESS CAMPAIGN
1979

PROGRESS REPORT CONCERNING THE ADVANCE NOTICE OF PROPOSED RULEMAKING ON WARNING LABELS ON CONTAINERS OF ALCOHOLIC BEVERAGES AND ADDENDUM

PS 011017

Printed for the use of the Department of Treasury,
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CONTENTS

Page

Text of
Progress Report: The Fetal
Alcohol Syndrome Public
Awareness Campaign 1

Addendum to Progress Report

A. "Scientific Review of Responses
to the Advance Notice of Proposed
Rulemaking: Warning Labels on
Containers of Alcoholic Beverages,"
by Gilbert S. Omenn, M.D., Ph.D.,
Robert Dixon, M.D., and John Ball,
M.D., from the Human Resources
and Social and Economic Services,
Office of Science and Technology
Policy, Executive Office of the
President, Washington, D.C. 21

B. THE FABRO REPORT: "Alcoholic Beverage
Consumption and Outcome of Pregnancy,"
by Sergio E. Fabro, M.D., Ph.D., from
the Fetal-Maternal Division, The George
Washington University Medical Center,
Washington, D.C. 35

C. THE HALL REPORT, letter to the Bureau
of Alcohol, Tobacco and Firearms from
Judith G. Hall, M.D., Division of Medical
Genetics, Children's Orthopedic Hospital
and Medical Center, University of Washington
School of Medicine, Seattle, Washington 201

D. THE ETZIONI REPORT: "A Systematic and
Graduated Response," by Amitai Etzioni,
Ph.D., Center for Policy Research, Inc.,
New York, New York 223

DEPARTMENT OF THE TREASURY

Bureau of Alcohol, Tobacco and Firearms

[27 CFR Parts 4, 5, and 7]

[Notice No. 318; Re: Notice No. 316]

THE FETAL ALCOHOL SYNDROME PUBLIC AWARENESS CAMPAIGN

Progress Report

AGENCY: The Department of the Treasury and the Bureau of Alcohol, Tobacco and Firearms (the Department).

ACTION: Progress report on the advance notice of proposed rulemaking (Notice No. 316; 43 FR 2186).

SUMMARY: The Department has concluded that there is a need for a public awareness campaign which educates the public about the possible dangers that consumption of liquor, beer, and wine by a pregnant woman can present to an unborn child. Because of the nature of the evidence now available as to the possible dangers, it is not yet clear that warning labels on alcoholic beverage containers would be the best tool to educate the public; and because the Department wants in all instances to avoid unnecessary government regulation, it is encouraging the alcoholic beverage industry to work with the Government and private interest groups to educate the public about the possible dangers. If, after a reasonable period of time, the Department does not find that these efforts to provide public information have been successful or that more precise medical evidence becomes available, the proposal to require a warning label on all alcoholic beverage containers will be reconsidered.

ADDRESSES: Copies of this progress report are available to interested parties by writing to:

Director
Bureau of Alcohol, Tobacco and Firearms
Post Office Box 385
Washington, D.C. 20044

(Attention: Chief, Regulations and Procedures Division; Notice No. 318)

Copies of the addendum to this progress report, which includes the experts' reports and the analysis from the the Office of Science and Technology Policy, the Executive Office of the President, are available for public inspection at the following reading rooms from 8:30 a.m. to 5:00 p.m.

BUREAU HEADQUARTERS

ATF Reading Room, Room 4408
12th and Pennsylvania Avenue, NW.
Washington, D.C.

CENTRAL REGION

ATF Reading Room, Room 6519
Bureau of Alcohol, Tobacco and Firearms
Federal Office Building
550 Main Street
Cincinnati, Ohio

MID-ATLANTIC REGION

ATF Reading Room, Third Floor
Bureau of Alcohol, Tobacco and Firearms
2 Penn Center Plaza
Philadelphia, Pennsylvania

MIDWEST REGION

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Bureau of Alcohol, Tobacco and Firearms
230 South Dearborn Street
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Bureau of Alcohol, Tobacco and Firearms
6 World Trade Center
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ATF Reading Room, Room 345
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Main Tower Building
1200 Main Street
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ATF Reading Room
Bureau of Alcohol, Tobacco and Firearms
3835 Northeast Expressway
Atlanta, Georgia

WESTERN REGION

ATF Reading Room, Thirty-fourth Floor
Bureau of Alcohol, Tobacco and Firearms
525 Market Street
San Francisco, California

FOR FURTHER INFORMATION CONTACT:

Charles N. Bacon or Armida N. Stickney
at 202-566-7626.

SUPPLEMENTARY INFORMATION:

I. BACKGROUND

The Bureau of Alcohol, Tobacco and Firearms (ATF) published in the FEDERAL REGISTER on January 16, 1978, an advance notice of proposed rulemaking concerning warning labels on containers of alcoholic beverages. This advance notice requested information to assist ATF in deciding whether the current regulations should be amended to require a warning label on alcoholic beverage containers, concerning the consumption of alcohol by pregnant women and the possible resulting birth defects in their newborn infants. ATF received over 3,000 comments from consumers, special interest groups, industry, doctors, and scientific researchers. The majority of those who wrote said they were opposed to a warning label.

The majority of these comments were from consumers (2,772). Most of the consumers opposed the warning label, particularly for wine containers. Industry members were also opposed to a warning label on the grounds that, at most, the fetal alcohol syndrome applies only to excessive users of alcohol and that the warning label would be costly and ineffective. The medical profession was divided on the issue; many practitioners felt that moderate use of alcohol during pregnancy has been beneficial while some researchers felt that there is clear evidence linking alcohol use by moderate drinkers to the fetal alcohol syndrome. Several objected, because warning labels would increase feelings of guilt by those women who had consumed alcohol during pregnancy and produced children with birth defects. A general consensus of those opposed was that it is the doctor's responsibility to advise about health hazards rather than the Government's and that any measure by the Government would constitute over-regulation. Many of the comments from doctors and consumers opposing warning labels originated from California, with at least 500 form letters coming from employees of wineries in California.

Those in favor of warning labels felt that alcohol consumption by pregnant women is potentially dangerous to their children and that a warning label would have a significant effect upon alcohol consumption by these women. They also felt that, in addition, a broad education program for pregnant women should be sponsored by both private concerns and the Government. Others, including women's groups, churches, alcoholism prevention groups, and social service agencies, thought that the proposal was a positive step forward and that a warning label would contribute to better health both for infants and for the public in general. It was also felt that consumers have a right to know what risks they are taking when they use a particular product.

Because of the conflicting and sometimes highly technical opinions offered as to the seriousness of the problem and as to the best method for approaching it, the Office of Science and Technology Policy, Executive Office of the President, was asked to evaluate the comments and evidence we received. They submitted an analysis

with a recommendation that the Department employ outside, specialized consultants to assess independently the warning label proposal and other approaches that would educate the public. Subsequently, we engaged three consultants in the following fields of expertise: (a) medical genetics, (b) obstetrics and pharmacology, and (c) social policy. None of these individuals have previously been involved in research or in formulating policy about the fetal alcohol syndrome problem.

The experts are Dr. Judith Hall, a medical doctor who is a specialist in genetics and Director of the Division of Medical Genetics at Children's Orthopedic Hospital in Seattle, Washington; Dr. Sergio Fabro, a medical doctor who holds advanced degrees in biological chemistry and pharmacology, and who is Professor and Director of the Fetal-Maternal Medicine Division, George Washington University Medical Center in Washington, D.C.; and Dr. Amitai Etzioni, a sociologist who is Director for the Center for Policy Research, New York, and now a Visiting Fellow at the Brookings Institution.

The Department provided two sets of questions for the experts, one of which was directed at the medical experts and the other at the social policy expert. Each of the experts was given copies of the comments received on the advance notice, and the record of the Senate Hearing before the Subcommittee on Alcoholism and Drug Abuse of the Committee on Human Resources, held January 31, 1978. The experts independently evaluated these materials and submitted written reports of their findings to the Department. These written reports were then sent to the National Institute on Alcohol Abuse and Alcoholism; the Food and Drug Administration; the Assistant Secretary for Health, the Department of Health, Education and Welfare; the National Academy of Sciences; and the Office of Science and Technology Policy, Executive Office of the President, for their comments.

II. SUMMARY OF EXPERTS' COMMENTS

A. FABRO REPORT.

1. Scientific Evidence.

Dr. Fabro conludes in this report that the fetal alcohol syndrome does exist. He states that "a series of rather aspecific abnormalities [central nervous system dysfunction; growth deficiencies; cluster of facial abnormalities; and variable major and minor malformations] have been grouped into a 'syndrome' which shows a remarkable reproducibility in that it has been observed only in offspring of chronic alcoholic mothers." He states that some alteration in brain function, growth, and facial appearance are essential for the diagnosis of the full-blown syndrome. He believes that evidence so far indicates that, to produce the full-blown syndrome, the level of alcohol consumption must be sufficiently high to cause easily-recognizable chronic alcoholism in the mother. He also states that, while evidence indicates that with lower levels of alcohol the full-blown syndrome is highly unlikely, "some other poor pregnancy outcome (e.g., low birthweight, stillbirth) appears possible." He thinks further, "Prospective epidemiological studies are required to establish whether, for example, wine (2-3 glasses) with dinner or one martini before dinner taken by the mother are devoid of any toxicity for the unborn child." Dr. Fabro believes that "the position taken by the March of Dimes in advising women about alcohol consumption and pregnancy is prudent. Until more data is accumulated in this respect, they advise any woman who is planning to become pregnant to abstain from consuming alcohol-containing beverages."

He thinks that heavy alcohol consumption by the chronic alcoholic mother appears essential for the occurrence of infants with the fetal alcohol syndrome, although the mechanism by which these adverse effects are produced is not known. He thinks that it is likely that ethanol in alcoholic beverages is the chemical responsible for producing the fetal alcohol syndrome; however, whether ethanol itself or one of its metabolites is the sole determining factor is not yet clear. Furthermore, the importance of other associated factors

likely to be present in heavily drinking women such as malnutrition, medical complications (e.g., delirium tremens, cirrhosis), and poor personal habits (cigarette smoking, caffeine intake, and drug abuse) has not yet been defined in regard to establishing the risk of the fetal alcohol syndrome in offspring of chronic alcoholic mothers. As far as the relationship of a woman's drinking pattern to pregnancy outcome is concerned, he thinks it is not known whether there is a critical period during or before pregnancy for the production of the fetal alcohol syndrome, nor is it known whether "binge" drinking is more important in the teratogenicity of alcohol than constant, persistent alcohol abuse, as in chronic alcoholic women. (A teratogen is a compound which causes malformations in the embryo or fetus when taken by the mother during pregnancy.)

He points out that laboratory tests of toxic effects of ethanol given to pregnant animals generally support findings of the toxic effect of ethanol during pregnancy. He cautions, however, against drawing firm conclusions based on animal studies since "at present there is no animal test or battery of tests that can predict human teratogenic risk with complete assurance."

He also points out that animal studies were probably the basis for the National Institute on Alcohol Abuse and Alcoholism's statement that "'there is substantial and serious risk for the fetus when the woman chronically drinks 3 or more oz. of absolute alcohol (6 drinks) a day.'" He said the selection of three ounces of absolute alcohol per day as the level when the risk begins to be substantial is an intelligent guess made by extrapolating animal teratological data into humans.

As far as the incidence of the fetal alcohol syndrome in children whose mothers are "moderate drinkers" is concerned, he says the full-blown syndrome has only been documented in offspring of chronic alcoholic drinkers although "some toxicity suspicious of, or compatible with, alcohol toxicity during pregnancy has been observed with lower (greater than 1 oz. absolute alcohol per day) consumption."

As for the effects of "binge" drinking, he thinks that "according to well-established pharmacological and toxicological principles, binge drinking, particularly during early pregnancy, may still theoretically be responsible for embryotoxic effects resulting in abortion, stillbirth, intrauterine growth retardation, and other anomalies which may be collectively termed 'embryotoxic alcohol related syndrome(s)' (EARS)."

2. Pros and Cons of Warning Labels.

Dr. Fabro declines to express an opinion on whether a warning label is justified, citing both incomplete data and his own lack of expertise on the effectiveness of such a measure. He does think, however, that any warning about the fetal alcohol syndrome should be directed at all women of childbearing age, rather than just pregnant women, since there are suggestions that alcohol consumption may exert toxic effects on the human embryo before the mother is aware that she is pregnant. He also thinks it is important to alert the corresponding male population as to possible toxic effects of alcohol on unborn children. Dr. Fabro said that effective prevention of the fetal alcohol syndrome may not be possible if doctors are solely responsible for informing women about the risks of drinking primarily because of the possiblity of danger in early stages of pregnancy before she visits the doctor. Ideally, he said, women should know about the dangers as they enter the childbearing years. Dr. Fabro suggests the possibility of explaining the risk during sex education classes in junior and senior high school.

3. Possible Adverse Effects of Warning Labels.

While Dr. Fabro does not directly address the question of whether warning labels would have adverse impact, he does say there is "no doubt that our knowledge in this area is scanty and that further research is needed."

B. HALL REPORT.

1. Scientific Evidence.

Dr. Hall finds the evidence "overwhelming" that the fetal alcohol syndrome exists as described by researcher Kenneth L. Jones et al.

(Jones' definition includes deficiencies in weight and length; delay of intellectual development and/or mental deficiency; poor coordination; changes in appearances of face, especially eyes; minor joint anomalies; valve defects of the heart; brain cell myragory abnormalities; and minor genital anomalies.) In addition to the full-blown syndrome, she thinks it is probable that "other more subtle deleterious effects occur in children whose mothers drink during pregnancy," the most serious of which are those which affect the brain and central nervous system. These effects are probably dependent upon the amount of the alcohol ingested, the timing during pregnancy, the genetic background of the mother and fetus, and other environmental factors such as smoking, nutrition, and medication. Dr. Hall says, "This second type of the maternal fetal alcohol spectrum has not yet been fully evaluated or delineated." She cites research studies which indicate "strong hints of behavioral differences, neurologic abnormalities, phychosocial illness...hyperactivity...in the offspring of moderate and binge drinking mothers; however, long-term follow-up of the infants born to mothers using moderate and minimal amounts of alcohol or those born to binge drinkers has not yet been possible."

Based on evidence available both from the studies on the fetal alcohol syndrome and other studies of human teratogens, she believes that "we will see this second category of defects manifested in the children of those women who drank alcohol during pregnancy, perhaps even very small amounts or only during critical periods." Dr. Hall thinks that the relationship between dose and fetal effect in humans will be difficult to establish in "self-reporting" studies, in part because alcoholics and others notoriously under report the amount they drink, and because there are very likely genetic variations affecting response to dose and timing of consumption. However, since other known human teratogens which cause malformations in large doses usually have an adverse effect in small doses as well, she believes the same kind of dose effect can be anticipated with alcohol. She estimates that the frequency of adverse effects may be as high as 1-2 per 100 births. Dr. Hall believes, "The most susceptible period for detrimental effects of alcohol on the fetus is probably in early pregnancy

(the first trimester)," but she claims that studies have also demonstrated adverse effects in later stages of pregnancy. Dr. Hall also points out, "Since one of the major effects of alcohol is on the developing brain and the brain continues to grow, neurons migrate and cells develop through all three trimesters, it seems likely (and there is some suggestion from the available data) that maternal alcohol consumption at any time during brain development could have an adverse effect."

Dr. Hall concludes that, given the present state of knowledge, "no minimum safe level of maternal alcohol consumption can be established at any time during pregnancy." She suggests that the most prudent advice to pregnant women is to avoid alcohol consumption during pregnancy and while nursing. She believes that the most serious time for alcohol consumption may be during very early pregnancy, prior to making the diagnosis of pregnancy.

2. Pros and Cons of Warning Labels.

Dr. Hall recommends that a warning label be required on containers and packaging materials of all alcoholic beverages. She believes women have the right to know that alcohol may endanger the unborn child, and that information about possible danger is not known either by the general public or, more importantly, by the medical profession. For those reasons, she also recommends that a broad educational program for the general public and health professionals be conducted. She states, "There is no question but [that] it is one of the most common known causes of mental retardation," and it is preventable.

She thinks it important that an educational program reach all women of childbearing age who may be considering becoming pregnant as well as their family members, husbands, and friends so they can be supportive of a woman's abstinence of alcohol. She thinks the question of previous effectiveness of labels (i.e., cigarettes) is irrelevant since no equivalent situation (a woman altering her behavior to protect her unborn child) has occurred.

3. Possible Adverse Effects of Warning Labels.

Dr. Hall finds two issues raised by those opposed to the advance notice which deserve consideration. The first issue is whether warning labels would produce unnecessary guilt in women who gave birth to a child (a) which had been damaged by alcohol or (b) which was mentally retarded for some other reason. Dr. Hall thinks this is an "unavoidable problem" and believes a parent would be "much more incensed and have more guilt if he or she was denied information that would have made it possible to avoid the problem."

The second issue is whether giving information directly to the women would interfere with the doctor-patient relationship. She believes most people are now health conscious and want to practice preventive health care, particularly pregnant women. She thinks that the data available from several studies suggest that moderate and "binge" drinking can be controlled and modified by the pregnant woman and that other studies also "suggest that even chronic alcoholics will try to curb their alcohol consumption in the interest of their unborn child." Dr. Hall is "concerned by the number of letters from physicians [in response to the advance notice] who indicated that they do not believe that alcohol can possibly have any adverse effect on the unborn child." She thinks "this attitude reflects the fact that the medical community is not fully informed about the effects of alcohol during gestation and further emphasizes that this information should be directly available to the public."

C. ETZIONI REPORT.

1. Scientific Evidence.

Dr. Etzioni, who is a sociologist, calls attention to the need for different public policies according to the way the ongoing research on the fetal alcohol syndrome unfolds. He believes different public policies are necessary if it is established that only high dosages, as against both high and low, are harmful; that only continuous drinking is harmful versus continuous and occasional ("binge") drinking; that harmful effects occur relatively late in the fetus

formation versus during the first two months. In some instances, only pregnant women will have to be reached, in others, all fertile women; in some instances, the target audience would be those who are relatively unresponsive (addicted drinkers), in other circumstances, the relatively more responsive social drinkers.

2. Pros and Cons of Warning Labels.

Dr. Etzioni believes the Federal Government should not treat this problem as an isolated issue but should view it as part of a systematic approach to public warnings. He believes warnings required by the Federal Government need to be graduated to differentiate clearly among levels of danger--according to strength of data available and magnitude of problem caused by the product at issue. He believes high alerts should be used sparingly, taking into account not just the costs which regulations and their enforcement entail, but "costs" in taxing the public's tolerance for government intervention.

He also believes as a matter of general principle "the stronger the data, the better the defense one can pose against criticism, and the easier it will be to legitimate the required warnings." He also thinks that "scientific data [need to] go through a sociological process in which they are publicly debated and a slow consensus emerges on the status of the data." He points out that this process is quite different from scientific evaluation, internal to the scientific community. He gives as examples of data that have been processed through the public: the definition of death as a flat brain wave pattern for 48 hours and the relative demerits of heroin versus marijuana. In contrast, he believes data about the fetal alcohol syndrome are not widely known, nor their implications much discussed yet. He, therefore, concludes that "the legitimacy of the claim that alcohol will damage a fetus is not at all well publicized. Regulation would more likely be respected if the data were first 'processed' more publicly...The fact that..data [on the fetal alcohol syndrome] at this stage are poorly processed suggests that the time is not ripe for relatively tough measures from this viewpoint. If higher levels of alert were desired on other

grounds, e.g., if new data suggested frequent [fetal alcohol syndrome] risk at early stages of pregnancy, then the public dialogue could be intensified. One of the most effective ways of doing this would be to foster some drastic measures (for instance, sending a registered letter from state health departments to all women aged 14 to 50, or at least to pregnant women, warning that alcohol may harm their fetus.")

He points to other considerations which do not favor a high-level alert. One is the effectiveness of warnings as a technique to deter people from behavior that could be harmful. He thinks warnings are more effective when people can switch to some other easily available substitute (from regular to filter cigarettes, birth control pills to other contraceptives, liquid protein diets to other diets). He thinks that warnings would be "more effective if it turned out that drinking wine or beer has no harmful effects on the fetus (a rather unlikely possibility), so that women could be advised to switch to these from hard liquor, or--if it turned out that women could be told to eat before they drink (to dilute the effects of alcohol). We expect warnings to be less effective the fewer 'near' substitutes are available."

Dr. Etzioni also thinks that warnings are less effective when both addiction and anxiety are present, which is very likely in the case when a woman is addicted to alcohol and anxious about the health of her unborn child. He goes on, however, to disagree with those who responded to the advance notice, saying that, because of the anxiety problem, information should be withheld so as not to generate more anxiety. "Women are not to be treated as neurotic, infantile creatures who need to be protected from tension. On moral grounds, it would be unethical to prevent millions of pregnant women from making an informed choice on the implausible idea that this bit of anxiety, in a world riddled with anxiety, would be the one that would tax their tolerance to the breaking point."

Dr. Etzioni points out that a number of comments submitted by industry suggested that the matter of alert be left largely to the doctor. He says "this reliance would be impossible if early

and moderate drinking have an effect, because then all women in fertile ages must be notified." He also points to studies which show that doctors have a poor record in transmitting such "preventive" information. He suggests that a broad-based public education program might be funded by adding one penny (or more) to the tax on alcohol and says that "public service announcements on television and radio may do more good than labels, although if one could have all the aforementioned and labels, they might benefit from the interaction effect...Public service announcements can be made to appeal more to motives, sentiments, and values, quite necessary in addition to, not instead of, informing, if people are to change their minds."

He says that he believes further scientific research is needed on the fetal alcohol syndrome before a decision to require warning labels is made. However, he says:

> If it is considered beneficial for pregnant women, their future children, and the public (which bears a good part of the resulting costs if the warning is ignored) not to consume alcohol, it will not be enough to merely inform women. It will also be necessary to help create a social climate which recognizes that it is unbecoming for a pregnant woman to drink. Thus, just as public service announcements try to break the idea that it is socially well-mannered to offer the driver "one more for the road," it will be necessary to establish that it is asocial to offer a drink to a pregnant women. Public service announcements and public educational campaigns, combined with the advice of physicians and other health professionals, are likely to be relatively more effective than labels or posters in bringing about this change in the social climate, although both of these might help.

3. Possible Adverse Effects of Warning Labels.

Dr. Etzioni thinks it important to consider the possible harmful effects that might follow a decision to require warning labels. He thinks it is possible that a "federal label on alcohol may well imply more approval of consuming it (at least by persons not pregnant) than is in the public interest. At least, the 'costs' of such federal legitimization of liquor should be weighed against the benefits of such labels."

He also thinks that there are growing segments of the public who ignore warnings, because "they feel they cannot heed the recent avalanche of forbiddens."

III. ANALYSIS AND CONCLUSIONS

Several conclusions can be drawn from the scientific data:

a. Heavy drinking by some women during pregnancy can result in a pattern of abnormalities in the offspring, called the fetal alcohol syndrome. This syndrome consists of specific congenital and behavior abnormalities including dysfunction of the central nervous system; growth deficiencies both before and after birth; cluster of facial abnormalities, especially the eyes; and mental retardation. The full-blown syndrome has only been identified in offspring of those women who are chronic alcoholics.

b. There is disagreement among our medical experts--which appears representative of differences within the scientific medical community--about the effects moderate, light, or "binge" drinking may have on the fetus. One expert says it is likely there is a linear relationship between the dose of alcohol and teratogenic effect down to one drink. The other expert does not believe that such a relationship has been proven. On moderate drinking, one expert points to studies which indicate that a mother's moderate drinking can cause a variety of physical and mental abnormalities in her offspring; and the other expert says the evidence is not clear.

However, both experts say in theory it is possible that "binge" drinking at the "wrong time" can be responsible for birth defects. Moreover, the two medical experts believe that absent clear evidence which establishes a safe level of drinking, the most prudent advice to women planning on becoming pregnant is to abstain totally from consuming alcohol from the time of conception to birth.

c. Studies indicate that pregnant women who are told of the danger alcohol can have on their children are amenable to changing drinking patterns during pregnancy.

d. There is a low level of awareness of the problem both on the part of the public in general and the medical profession.

The Department believes there is sufficient evidence to require further action on the part of industry and Government to educate the population at large, and particularly women of childbearing age, about the problem. The potential consequences are both real and preventable; and most people, including many doctors, are generally unaware of the state of scientific knowledge. We agree with the experts' unanimous opinion that responsibility for informing women of the possible risks should not be left solely to a woman's doctor. The scope of education must be broader than the woman who thinks she may be pregnant and therefore consults a doctor. Initially, risks exist at the earliest stages of pregnancy before a doctor has been consulted and some, particularly low income women, never seek prenatal care. We also agree with the experts' advice that efforts be made to educate the potential male parent so that he can participate in, and be supportive of, any decision as to alcohol consumption during pregnancy. We also agree that special efforts should be made to reach the teenage population because of the recent increases in teenage pregnancies and drinking.

One option which has been considered is to require a warning label concerning the risks of alcohol for the pregnant woman on all alcoholic beverage containers. The Department believes that adequate statutory authority exists for such a

requirement and that, in many cases, labeling has served as a vehicle for communication. Such an approach would bring some information about this issue to the attention of large segments of the drinking population.

In the case of the fetal alcohol syndrome, however, we have concluded that other forms of education should be attempted before deciding on the necessity of labeling. It seems that warning labels can be most effective when the message sought to be conveyed is simple and easy to state. In the case of the fetal alcohol syndrome, however, the state of scientific evidence does not lend itself to such directness. There are differences of opinion as to the important issues of "binge," moderate, and one-time drinking which cannot be ignored if the message to be communicated is to be as accurate as it should be. Other forms of education--which explain more fully the scientific issues involved--may in this situation be more effective than warning labels and still provide a basis for educated, consumer decision-making.

It is also important, generally, that warnings not overstate the danger being discussed. We feel that any action plan should consider the fact that it may be unfair to cause people to think that any level of drinking in pregnancy (i.e., one drink) may have caused problems such as mental retardation in their children. Any approach, therefore, must insure that the information which is disseminated is as accurate as possible.

We are also not unmindful of the analysis of Dr. Etzioni discussed above concerning the process, impact, and effectiveness of government warnings. It is possible that education not so directly prescribed by the Government may be as, or more, effective than the simple issuance of what some may consider to be just another government warning. Moreover, we also believe that, where appropriate, Government should first allow the private sector the opportunity to take action before mandating a specific approach by rule. In this case, for example, a sense of corporate responsibility and the desire to avoid potential legal liability and future regulation may motivate sufficient actions.

IV. PLAN OF ACTION

The Department thus intends to work with other appropriate Federal agencies (i.e., the Department of Health, Education and Welfare, including the Food and Drug Administration and the National Institute on Alcohol Abuse and Alcoholism), and with members of all segments of the alcoholic beverage industry, and with other interested groups to develop and implement a program of public education. Among the steps we believe should be included in these education programs are:

a. Publishing and distributing this report and those of the retained experts to segments of the public, medical schools, and interested organizations;

b. Publishing and disseminating brochures for the public and the medical profession;

c. Stimulating education programs in schools;

d. Developing public service television and radio announcements; and

e. Issuing press releases.

The Department intends to monitor carefully the impact of these efforts. We recently conducted an independent public opinion poll to measure the current level of public awareness concerning this problem. In about six months to a year, a new poll will be conducted to compare the level of public awareness. After the two polls are analyzed, a judgement will be made as to the sufficiency and impact of the private and the Government's education programs which have been undertaken.

If the evaluation of the joint industry-Government public awareness campaign indicates that there is not a sufficiently high level of public awareness of the problems associated with the drinking of liquor, beer, and wine, particularly among women of childbearing age, or if more precise medical evidence is developed in current or future studies, then the Department will again consider

requiring a warning label as a means of direct communication of this and possibly other health problems to the public.

V. DRAFTING INFORMATION

Officials from the Department of the Treasury and the Bureau of Alcohol, Tobacco and Firearms jointly participated in developing this progress report.

VI. AUTHORITY

Accordingly, this progress report is issued under the authority contained in section 5 of the Federal Alcohol Administration Act, 49 Stat. 981, as amended (27 U.S.C. 205).

Signed: January 23, 1979

/s/ John G. Krogman

John G. Krogman,
Acting Director
Bureau of Alcohol, Tobacco and Firearms.

Approved: January 25, 1979

/s/ Richard J. Davis

Richard J. Davis,
Assistant Secretary
(Enforcement and Operations).

ADDENDUM

A. "SCIENTIFIC REVIEW OF RESPONSES TO THE ADVANCE NOTICE OF PROPOSED RULEMAKING: WARNING LABELS ON CONTAINERS OF ALCOHOLIC BEVERAGES."

Washington, D.C.

May 1, 1978

Scientific Review of Responses to the Advance Notice of Proposed Rulemaking: Warning Labels on Containers of Alcoholic Beverages

Effects of Alcohol on the Fetus

For more than two hundred years, articles have appeared in the literature suggesting a correlation between alcohol and mentally defective offspring.[1] In 1968, Lemoine and co-workers published in a French medical journal[2] work on a malformation syndrome found in offspring of female alcoholics, but this germinal research did not initially find its way into the English language literature and received little attention. The teratogenic effects of alcohol were independently rediscovered in 1973 when Jones et al. reported the effects of alcoholism on human fetal development,[3] describing a set of signs and symptoms they termed the "fetal alcohol syndrome" (FAS)*.[4] The principal features of the syndrome are distinctive, and involve central nervous system dysfunction, linear growth deficiency before and after birth, and underdevelopment of the mid-face, especially the eyes. In addition to these malformations or morphologic defects, mental retardation was soon discovered to be a prominent characteristic of children with the syndrome, the degree of retardation generally varying with the degree of physical malformation.[5] The importance of these findings was obvious. The possibility of defining the etiology of mental retardation of a significant portion of children engendered great interest and, thus, stimulated a number of studies, several of which are still in progress.[6]

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*While FAS has received the most attention in this review, it should be noted that alcohol produces a number of adverse effects on the fetus other than FAS, including decreased birth weight and increased number of stillbirths.

Studies using at least six different laboratory animal species have demonstrated that alcohol not only produces congenital malformations but biochemical and behavioral alterations of offspring as well.[7] In addition, neuropathologic studies of the brains of offspring exposed *in utero* to high concentrations of alcohol show widespread malformation.[8]

The findings of Jones *et al.* were followed by a series of case reports of abnormal physical features suggestive of FAS in offspring of alcoholic mothers. Hanson, in 1976, reported 41 cases of FAS and noted an additional 37 cases identified elsewhere.[9] Today, over 200 cases of FAS have been reported from more than 20 medical centers around the world.[10,11] In published reports, the incidence of FAS has been found to be 1-2 per 1,000 live births; expression of some of the syndrome's characteristics occurs at least twice as frequently.[11] Thus, fetal exposure to alcohol may be a major cause of mental retardation.

Relation to Quantity Ingested by the Mother

Quantification of the levels of alcohol consumption associated with FAS has been especially difficult.[12] That difficulty lies primarily in reliance on a single retrospective interview assessment of a woman's drinking history, and is exacerbated considerably by the general tendency of respondents to underestimate consumption. It is particularly true that heavy drinkers underestimate consumption. In several studies,[13,14,15] only about 5 to 10% of pregnant women report consumption of more than one ounce of absolute alcohol per day. In general, studies define the threshold

of "heavy" drinking at this level, although some also include in the definition the consumption of 5 or more drinks on occasion (so-called "binge" drinking).**

While it is difficult to make a firm estimate, the risk of the development of the full fetal alcohol syndrome in an offspring of a heavy drinker (as defined above) is probably in the 1-4% range. The relation of dose to the development of the syndrome or any adverse effect is frustrated by the complexity of such variables as the determination of an accurate history of the amount of consumption, the character of intake (at regular intervals or sporadic), the rate of metabolism, and the effect of other agents, such as cigarettes. Even more difficult is the determination what level is "safe." In fact, both the National Council on Alcoholism and the National Foundation/March of Dimes stress that the only safe decision for expectant mothers is not to drink during pregnancy.[19,20] More importantly perhaps, at least one investigator notes that the strongest relationship between maternal alcohol consumption and fetal outcome seems to be drinking behavior in the mother between the time of conception and of recognition of pregnancy.[21]

Effectiveness of Labeling

No good data exist with regard to the effectiveness of labeling alcoholic beverages. It is, however, generally true that pregnancy is a time when women become most concerned about their bodies and are most

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**Most studies use the questionnaire developed by Jessor[16] to estimate alcohol use. This instrument measures the average daily ounces of absolute alcohol (AA) ingested: this value is termed the "AA score." An "AA score" of 1.00 is equivalent to 1 ounce of absolute alcohol or 2 ounces of 100-proof whiskey. Some use the Cahalan "volume-variability" index:[17] heavy drinkers are those who consume a minimum average of 1½ drinks per day and at least 5 or 6 drinks on some occasions.

amenable to undertaking good health practices.[15] In addition, there is evidence that women who drink decrease the amount they drink after learning they are pregnant[13] and the sporadic or binge drinker may significantly alter this potentially hazardous pattern. Although it is clear that heavy drinking during pregnancy is associated with the fetal alcohol syndrome and that abstinence is not, the data are conflicting with regard to the effect of stopping drinking after the first trimester. Streissguth, for example, has suggested that fetal structural effects may occur very early in pregnancy.[22] On the other hand, preliminary data of Rosett et al. suggest that abstinence or marked reduction of alcohol use during the second half of pregnancy can lower the risk of defective offspring.[15] Thus, some evidence exists to suggest that there is a subgroup of drinkers -- pregnant women -- who are amenable to decreasing consumption, and that, if they in fact decrease consumption, they may decrease the risk of fetal malformation and mental retardation.

Whether, however, labeling would have any desired effect is open to question. No evidence which directly addressed the question was presented for review. Anecdotal evidence exists that in a possibly analogous situation -- the labeling of cigarettes -- there was initially a decrease in consumption but that present consumption is now as high as before labeling. Several respondents stated their opinion that labeling would be valueless.

A final issue concerns the possible adverse health effects of labeling, two such possibilities being raised by the respondents. One was that labeling represented an intrusion in the doctor-patient relationship.

A counterpoint to that concern is that there exists precedent in the requirement by the Food and Drug Administration of "patient package inserts" -- informational literature attached to certain drugs. The second concern was that the existence of labeling would increase feelings of guilt in the woman who does not decrease consumption and who bears a retarded or malformed infant. On the other hand, it is likely that feelings of hostility and frustration would be at least as great if the woman were unaware of the ill effects of alcohol to the fetus until after birth. No data were presented to support or refute this concern.

Conclusions

1. It is clear that heavy drinking by some pregnant women produces signs of fetal alcohol syndrome in their offspring.
2. Data exist that moderate drinking by pregnant women also causes a variety of physical and mental abnormalities in their offspring.
3. The threshold of alcohol consumption required to produce any change is not certain. Conversely, it is not possible at this time to certify a safe level or drinking pattern.
4. It is likely that pregnant women are amenable to changing poor health habits.
5. The effectiveness of labeling of alcoholic beverages is not certain.

Recommendation

Because of the clinical, political, and regulatory complexity of the issue of labeling of containers of alcoholic beverages, the Office of Science and Technology Policy recommends that a small group of qualified uninvolved consultants be convened to review the available material concerning the issue, and to make recommendations regarding the proposed labeling.

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ADDENDUM

B. THE FABRO REPORT: "ALCOHOLIC BEVERAGE CONSUMPTION AND OUTCOME OF PREGNANCY."

Washington, D.C.
September 25, 1978

PREFACE

This document is a written report to the Bureau of Alcohol, Tobacco, and Firearms on the scope of ATF's Fetal Alcohol Syndrome Program, as defined in Contract ATF-78-C-1086.

In reviewing the twelve volumes of materials received from the Department of the Treasury, as well as additional available data on maternal alcohol intake and pregnancy outcome, it became evident that there are number of problematic areas in this subject. Although most of them are interrelated, I have attempted to analyze each problem individually, at the expense of some repetition. To this end, after a general introduction, the material presented is divided into 4 main sections.

The first section (Section A) contains a review of the available data relating to pregnancy outcome in chronic alcoholics. In addition, this section summarizes evidence obtained thus far in laboratory animals on the toxicity of ethanol during pregnancy.

Section B deals with an evaluation of the available data according to known pharmacological, toxicological, teratological, and epidemiological principles, followed by the Summary and Concluding Remarks (Section C).

Section D deals with the answers to the FASP Questionnaire, and is followed by the Bibliography (Section E).

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INDEX

		PAGE
Preface		37
Acknowledgements		38
Index		39
Introduction		40
SECTION		
A-1	Pregnancy Outcome in Women with Medically Recognized Chronic Alcoholism	43
A-1, a	The Fetal Alcohol Syndrome	43
A-1, b	Epidemiological Studies in Chronic Alcoholic Women	51
A-2	Epidemiological Studies on the Effects of Maternal Alcohol Consumption on Pregnancy Outcome	53
A-3, a	Studies in Laboratory Animals	65
A-3, b	Comments	77
A-4	Summary	82
B-1	Pharmacological and Toxicological Principles	83
B-1, a	Pharmacology of Alcoholic Beverages	83
B-1, b	Clinical Manifestations of Alcoholism	96
B-1, c	Pharmacological and Toxicological Principles of Alcohol Consumption and Pregnancy Outcome	107
B-2	Teratological Principles	111
B-3	Epidemiological Principles	126
C	Summary and Concluding Remarks	147
D	FASP Questionnaire	151
E	References	176

INTRODUCTION

Intemperance in the use of alcoholic beverages creates many problems in modern society. These problems may be divided into three categories: psychologic, medical, and sociologic. The chief psychologic problem is why a person drinks excessively, often with full knowledge that such action will result in physical injury to himself and irreparable harm to his family. The medical problem embraces all aspects of alcoholic habituation as well as the diseases which result from over-indulgence in alcohol. The sociologic problem comprises the effects of sustained inebriety on the family and community.

Alcoholism has been defined as both a chronic disease and a disorder of behavior, characterized in either context by drinking alcohol to an extent that surpasses the social drinking customs of the community and that interferes with the drinker's health, interpersonal relations, or means of livelihood. Reduced to pharmacologic terms, it is addiction to alcohol.

TABLE I.

ESTIMATED PATTERNS OF AMERICAN ADULT DRINKING PRACTICES

	TOTAL		MALE		FEMALE	
	POPULATION (Millions)[2]	PER CENT[3]	POPULATION (Millions)	PER CENT	POPULATION (Millions)	PER CENT
All Persons Age 18+[1]	149.5	100	71.2	100	78.2	100
Abstainers	47.8	32	16.4	23	31.3	40
Infrequent Drinkers[4]	15.0	10	5.7	8	8.6	11
Light Drinkers[5]	46.3	31	21.4	30	25.8	33
Moderate Drinkers[6]	26.9	18	17.1	24	9.4	12
Heavy Drinkers[7]	13.5	9	10.7	15	3.1	4

[1]Categories by sex and type of drinker do not add to totals due to rounding.

[2]Population estimates for July 1, 1976 from Bureau of Census.

[3]Proportionate drinking category estimates for adults age 18+ from Harris Surveys 1972-1974.

[4]Drink less than once per month.

[5]Drink less than 0.22-oz. absolute alcohol per day.

[6]Drink 0.22 - 1.0-oz. absolute alcohol per day.

[7]Drink more than 1.0-oz. absolute alcohol per day.

NCALI

Compiled by the National Clearinghouse for Alcohol Information.

EXAMPLES OF DAILY CONSUMPTION

	Beer		Wine		Liquor
Light Drinking	less than 6-oz.	OR	less than 2-oz.	OR	less than 0.5-oz.
Moderate Drinking	6 - 27-oz.	OR	2 - 9-oz.	OR	0.5 - 2.5-oz.
Heavy Drinking	more than 27-oz.	OR	more than 9-oz.	OR	more than 2.5-oz.

RS 77-03

The precise number of such persons, commonly called alcoholics in the United States is not known. In 1971, the Department of Health, Education, and Welfare estimated that about 9 million men and women (7 percent of the adult population) "manifested the behavior of alcohol abuse and alcoholism." According a recently issued report by the National Institute of Alcohol Abuse and Alcoholism, as of July 1, 1976, there were 13.5 million heavy drinkers in this country.

In the late '60's and early '70's, attention turned to a specific aspect of the multiple problems created by alcohol abuse. Lemoine et al. (1) in 1968, and Jones and his associat in 1973 (2), described a specific dysmorphic syndrome - the Fetal Alcohol Syndrome (FAS) - in offspring of chronic alcoholic mothers and this dramatically sharpened the focus on the relationship between ethanol intake by the pregnant woman and the health of the infant.

SECTION A-1: PREGNANCY OUTCOME IN WOMEN WITH MEDICALLY RECOGNIZED CHRONIC ALCOHOLISM

It has been known for centuries that the infants of chronic alcoholics are likely to be born "weak and sickly and often look shrivel'd and old, as though they have numbered many years" (3). However, no precise account was given until recent times when Lemoine (1) in France in 1968 and Jones and Smith (2) in 1973 in the U. S. A. described a specific dysmorphic condition, the Fetal Alcohol Syndrome (FAS) characteristic of offspring of chronic alcoholic mothers.

SECTION A-1, a: The Fetal Alcohol Syndrome (FAS)

By 1976, only three years after Jones' original article, well over 200 cases of infants with FAS had been described in the literature (4), and in almost all cases chronic alcoholism was recognized in the mother during pregnancy. The account of the FAS given below is taken from the reports originating from the Dysmorphology Unit of the University of Washington in Seattle.

According to Clarren and Smith (4), the abnormalities most typically associated with the FAS can be grouped into four categories (Table 2): 1) central nervous system dysfunction; 2) growth deficiency; 3) a characteristic cluster of facial abnormalities; and 4) variable major and minor malformations.

Table 2: Principal Features of the Fetal Alcohol Syndrome Observed in 245 Persons Affected (4)

FEATURE	MANIFESTATION
Central nervous system dysfunction:	
Intellectual	Mild to moderate mental retardation*
Neurologic	Microcephaly*
	Poor co-ordination, hypotonia+
Behavorial	Irritability in infancy*
	Hyperactivity in childhood+
Growth deficiency:	
Prenatal	<2 SD for length & weight*
Postnatal	<2 SD for length & weight*
	Disproportionately diminished adipose tissue+
Facial characteristics:	
Eyes	Short palpebral fissures*
Nose	Short, upturned+
	Hypoplastic philtrum*
Maxilla	Hypoplastic+
Mouth	Thinned upper vermilion*
	Retrognathia in infancy*
	Micrognathia or relative prognathia in adolescence+

*Feature seen in > 80% of patients.

+Feature seen in > 50% of patients.

Central nervous system dysfunction - Mental retardation has been one of the most common and serious problems associated with ethanol teratogenicity. In 126 patients with FAS in which performance was evaluated according to standardized testing procedures, 107 (85%) scored more than two standard deviations below the mean (5, 6, 7, 8, 9, 11, 12, 13). While not all affected individuals were retarded, rarely did an affected patient display average or better than average mental ability. Whether the mental deficiency in these patients is the result of prenatal exposure to ethanol or is the consequence of post-

natal life with an alcoholic mother must be carefully considered. However, evidence has now accumulated to support a prenatal origin for much of the problem.

Streissguth et al. (13) have evaluated intelligence in 20 patients with FAS who had varying degrees of growth deficiency and dysmorphic features. The patients ranged in age from 9 months to 21 years. The average I. Q. was 65 with a range from 16 to 105. In general, the more phenotypically involved individuals had the lower I. Q. scores, suggesting that the prenatal insult which produced the dysmorphic features also produced the mental deficiency.

Jones et al. (14) found in a survey of the offspring of 23 chronically alcoholic women from the Perinatal Collaborative Project of the National Institutes of Neurologic Diseases and Stroke that 44% of the surviving offspring had I. Q. scores which were below 80. Intelligence scores were not statistically different between those children raised with their alcoholic parents and those raised by relatives or in foster homes.

Clarren et al. (15) have recently demonstrated structural alterations in the brains of infants exposed to alcohol in utero. Four brains showed similar malformations related to failure or interruption of neuronal and glial migrations. While the type of malformation was similar in each case, the location of the malformations varied from subject to subject. The most consistent anomalies were cerebellar dysplasias and heterotopic cell clusters, especially on the brain surface. In

one instance, the malformations were primarily in the cerebrum and there was associated microcephaly. Subtentorial anomalies produced hydrocephalus in two cases but had no untoward effects on head size in another patient. Similar malformations have been described by Majewski in one patient (16).

Microcephaly has been an important feature of the FAS. Generally it has been of prenatal onset, although occasionally it has only become apparent with time. Microcephaly reflects deficient brain growth but as the neuropathologic and psychologic studies demonstrate, normocephaly does not necessarily predict normal brain structure or function after intrauterine alcohol exposure. Furthermore, hydrocephaly can be an occasional variant in FAS if the malformations which usually cause limited brain growth also interfere with cerebrospinal fluid dynamics (4).

Neurologic abnormalities may be present from birth in FAS, indicating the prenatal nature of this condition. Newborns are usually irritable, tremulous, have a poor suck and have apparent hyperacusis (5, 17). These abnormalities usually last several weeks or months. Older children have most frequently shown hypotonicity (5, 8, 13, 20, 21). However, severe hypertonicity has been observed in at least one older patient (22) and mixed tonicity with hypotonic arms and hypertonic legs has been noted in one other case (23). Seizures beyond the neonatal period have been surprisingly rare, although neonatal seizures have been occasionally observed (17, 22, 24).

Hyperactivity is a frequent component of FAS in young children. The extent to which this behavior is organic versus environmentally determined has not been established.

Growth deficiency - Most infants with FAS are growth deficient at birth for both length and weight. Jones and Smith observed greater deficits in prenatal linear growth than in weight at birth in their initial Seattle patients (2), but it has now been recognized that many affected infants have greater deficits postnatal weight than length. Few infants have demonstrated postnatal catch-up growth. With their poor suck and poor growth, many affected infants have been initially and repeatedly evaluated for failure to thrive. In general, children with FAS remain more than two standard deviations below the mean for height and weight with weight being more severely limited.

Decreased adipose tissue is a nearly constant feature of children with FAS. A major complaint of parents bringing their children to clinic for follow-up has been their inability to "fatten up" their "skinny little kid" (4).

Although failure to grow at a normal rate has prompted some endocrinologic studies, appropriate levels of growth hormone, cortisol and gonadotropins have been demonstrated in FAS children (11, 25).

Distinctive facial abnormalites - there is a rather typical facial appearance in persons with the fetal alcohol syndrome. While many disorders include mental deficiency and growth deficiency, it is the facial similarities among FAS children which unite them into a discernible entity. While these similarities are clear from the

photographs of affected children published by numerous authors, the written descriptions have not always emphasized the same features, and this has led to some ccnfusion. The fetal alcohol syndrome facies is characterized by a few key features: short palpebral fissures, a hypoplastic upper lip with thinned vermilion, and diminished to absent philtrum. Frequently the face is further altered by midfacial growth deficiency and mandibular growth deficiency.

The growth of the eye, as of the rest of the nervous system, is adversely affected by fetal alcohol exposure. On rare occasions, eye growth has been so deficient that frank microphthalmia has been seen (5). Typically, modest growth deficiency of the eye is reflected in shortened palpebral fissures. Unfortunately, standards for palpebral fissure size in children are based on rather old data and the means and standard deviations are inadequately established (26, 27). Clarren and Smith (4) have viewed short palpebral fissures as one of the most important diagnostic criteria; thus, 59 of their FAS patients (91%) have had this facial feature. Twelve other authors have described short palpebral fissures in 54 of 74 patients (73%). Only Majewski did not find this abnormality to be a frequent feature. He reports short palpebral fissures in less than 10% of his 76 patients (16). Strabismus and myopia are frequent eye prblems. Majewski (20) has reported ptosis in 50% of his patients and blepharophimosis in 10%, but these abnormalities

have been less frequently noted by other observers. Structural alterations within the eye such as cataracts, optic atrophy, and tortuous retinal vessels have been observed in individual cases.

The face, in general, has a drawn appearance. This is produced principally by the thinned upper vermilion and hypoplastic philtrum, and is further accentuated by the frequent additional feature of midface hypoplasia. The retrusive maxilla contributes to the accompanying flattened profile and occasional downslanting of the palpebral fissures. The nose is frequently short with a low bridge and associated epicanthal folds and anteverted nostrils. The short upturned nose gives the real or apparent impression that the distance from the alae nasae to the upper lip is long. Cleft lip and palate have been occasionally observed.

The ear and mandible are involved in some patients. Posterior rotation of the helix is common and alteration in conchal shape occurs occasionally. The mandible is generally small at birth. In some children, micrognathia remains with increasing age, in others the jaw grows relatively better than the midface and an apparent prognathism may be seen in adolescence.

Taken as a whole, the face of fetal alcohol syndrome is as distinctive as that of Down's syndrome and is as readily appreciated in the newborn period as in later life. However, the important abnormalities, taken individually, are subtle and not likely to be found in standard listings of malformations.

Associated major and minor anomalies - While there is an increased frequency of malformations in children with FAS, no one major malformation occurs in the majority of cases. Table 3 lists the major and minor malformations which have been found in at least 2 of the available 245 reports.

Table 3: Associated Features of the Fetal Alcohol Syndrome Observed in 245 Persons Affected (4)

AREA	FREQUENT*	OCCASIONAL+
Eyes	Ptosis, strabismus, epicanthal folds	Myopia, clinical microphthalmia, blepharophimosis
Ears	Posterior rotation	Poorly formed concha
Mouth	Prominent lateral palatine ridges	Cleft lip or cleft palate, small teeth with faulty enamel
Cardiac	Murmurs, especially in early childhood, usually atrial septal defect	Ventricular septal defect great-vessel anomalies, tetralogy of Fallot
Renogenital	Labial hypoplasia	Hypospadias, small rotated kidneys, hydronephrosis
Cutaneous	Hemangiomas	Hirsutism in infancy
Skeletal	Aberrant palmar creases, pectus excavatum	Limited joint movements, especially fingers & elbows, nail hypoplasia, especially 5th, polydactyly, radioulnar synostosis, pectus carinatum, bifid xiphoid, Klippel-Feil anomaly, scoliosis
Muscular		Hernias of diaphragm, umbilicus of groin, diastasis recti

* Reported in between 26 and 50% of patients.
+ Reported in between 1 and 25% of patients.

Differential diagnosis - In a few severely affected children, a superficial facial resemblance to deLange syndrome has been noted (4, 6). Two children with gestational histories of substantial ethanol exposure have also been reported to resemble patients with Noonan syndrome (30, 31). Generally, however, the FAS phenotype is distinct and not readily confused with other recognized patterns of malformation.

SECTION A-1, b: Epidemiological Studies in Chronic Alcoholic Women

Two studies have been reported on the outcome of alcoholic pregnancies, but the sample size in both is small. Shurygin (32) described 42 children born to 18 alcoholic mothers in Russia. The 19 offspring born prior to the mothers' alcoholism displayed disorders that were primarily "vegetative, emotional and behavioral" with symptom onset at 9-10 years of age and symptom remission with improved social circumstances. On the other hand, many of the 23 children born after full-fledged alcoholism in the mothers had "profound impairments of the CNS that were manifest early in infancy." Fourteen of these 23 were mentally retarded. Unfortunately, little is known regarding the socio-economic or educational status of the families, but it was noted that there were not serious somatic diseases in the mothers, nor materially inadequate circumstances for the children.

The second systematic study of offspring of alcoholic mothers was obtained by a review of the charts of the National Institute of Neurologic Disease and Stroke's Perinatal Project

(14). This has been a prospective study of about 55,000 women and their offspring who had been observed up to seven years postnatally in 12 medical centers. Unfortunately, direct questions about alcohol use during pregnancy had not been included in the original research design. However, whenever alcoholism was mentioned in the clinical record, a retrospective entry had been made in the chart summary. Charts were reviewed and in 23 cases there was evidence of chronic alcoholism before and during the pregnancy. Each of these was compared with charts of two non-alcoholic control women matched for socio-economic status, education, race, age, parity, marital status, and the institution where the mother and child were followed. Charts of the offspring were reviewed by another investigator who had no information about the mothers' drinking status. Among the offspring of the alcoholic women, there were four who died in the perinatal period and six who had physical findings consistent with the FAS. Thus, the rate of adverse outcome was 43% as compared with a 2% rate in the control group. Offspring of the alcoholic women had smaller growth parameters in the newborn nursery as well as at seven years of age. I.Q. testing at age seven was available in 12 offspring of the alcoholic women. Of the 12, the six who had lived with their mothers had a mean I.Q. of 73, while the six who had spent some time with relatives had a mean I.Q. of 84.

SECTION A-2: EPIDEMIOLOGICAL STUDIES ON THE EFFECTS OF MATERNAL ALCOHOL CONSUMPTION ON PREGNANCY OUTCOME

A number of epidemiologic studies have been initiated in an attempt to establish a relationship between level of alcohol consumption by the mother and pregnancy outcome. Unfortunately, these studies utilized a variety of different techniques to measure alcohol consumption in relation to light, moderate, and heavy drinkers. Not all of the studies are epidemiologically well controlled for confounding factors, and different end-points were sometimes measured. Comparisons among these studies are therefore difficult and discordant results may be expected. Of course, this also raises the question of the validity of applying the results of such studies to entire populations.

In a fairly well-controlled study, Little (28) used a quantity-frequency-variability questionnaire to determine average ounces of absolute alcohol consumed per day. She found that maternal alcohol use in the six months prior to pregnancy and in the fifth through the eighth month of pregnancy was significantly related to birth weight of offspring after controlling for maternal age, height, parity, and smoking, as well as gestational age and sex of offspring. She used a sample of 263 women with single live births without medical complications, all middle class, predominantly white, and participating in a health maintenance organization. Daily consumption of one ounce of absolute alcohol per day in the

pre-pregnancy period was associated with an average weight decrement of 90.8 grams in the offspring. This amount consumed in late pregnancy was associated with a 160 gram decrement in birth weight.

Kaminski, Rumeau-Rouquette and Schwartz (33) reported similar finding of 9,236 pregnant women studied in Paris. Women consuming over 0.4 liters of wine or an equivalent daily (approximately 1.5 oz. of absolute alcohol) had more stillbirths, higher rate of small-for-date babies, lower average placental weight and infants with lower average birth weight. These findings were significant even when other risk factors related to alcohol consumption were controlled for. Beer drinking seemed to be particularly implicated in the increased risk, compared to wine drinking.

Ouellette, Rosett, Rosman and Wiener (34) in a prospective study of drinking and the outcome of pregnancy in 322 predominantly non-white, high risk, inner-city women, also reported a significant relationship between heavy alcohol use and intrauterine growth retardation and abnormality in the offspring. Thus, infants born to heavy drinkers had twice the risk of an abnormality as compared to those born to abstinent or moderate drinkers. Thirty-two percent of infants born to heavy drinkers demonstrated congenital anomalies, as compared to 9 percent in the abstinent and 14 percent in the moderate group. Microcephaly and multiple congenital anomalies were much more frequent in this group. Women classified as heavy drinkers in this sample had a much higher alcohol intake than those of Little or Kaminski.

Two epidemiological studies failed to find a relationship between alcohol intake during pregnancy and birth weight of offspring (35, 36). Mau and Netter (35) did, however, report a significant relationship between coffee ingestion (in the first trimester) and birth weight of offspring and also between alcohol consumption (in the first trimester) and shorter gestations. They attempted to control for related factors including maternal age, parity, socioeconomic status, and body weight, by analyzing appropriate subsamples. They reported that the alcohol and coffee effects appear independent of most such factors.

A retrospective epidemiologic study of intrauterine growth was conducted by Russell (37), who reviewed records of women attending a county hospital outpatient clinic. She hypothesized that women with an alcohol related psychiatric diagnosis were more likely to have been drinking heavily during a prior pregnancy than either women selected at random from the general population, or women with a psychiatric diagnosis that was not alcohol related. Birth weights of 223 offspring of 81 women with an alcohol related diagnosis were obtained from birth certificates and compared with the birth weights of 276 offspring of 94 women with a non-alcohol related diagnosis. Each of these offspring were matched with a control selected from birth certificate files employing criteria of sex, county of birth, year of birth, maternal age, race, and education. The birth weight of each infant born to an alcoholic woman was subtracted from that of the matched control infant and these

differences were analyzed with respect to maternal drinking histories. Russell found that the average birth weight of infants born to women with an alcohol related psychiatric disorder was significantly lower than that of infants born to other women seen in the clinic. No congenital malformations were recorded on the birth certificates of the study children, and only one malformation was recorded on those of matched controls. Drinking histories could be estimated from clinical records for 95 women, not all of whom had been diagnosed as having alcohol related psychiatric problems. When mothers started drinking more than 11 years before delivery, the mean birth weight was 898 grams less than matched controls ($p < .01$); 6-10 years of maternal drinking, 403 grams ($p < .01$); 0-5 years, 319 grams ($p < .05$). Drinking by fathers was not associated with lower birth weights.

Three prospective studies on alcohol and pregnancy outcome have been underway in the United States for the past three years, and two of these have focused on a variety of individual infant assessments in addition to the usual pregnancy outcome variables used in epidemiological studies.

The Boston University Study (34, 38) - A collaborative program was initiated in May 1974, by the Departments or Obstetrics and Gynecology, Pediatrics, Pediatric Neurology, and Psychiatry of the Boston University School of Medicine and the Boston City Hospital. In this study, the sample was a high risk inner-city group with a high proportion of non-white and non-married subjects.

Cahalan's volume-variability index was used to evaluate alcohol consumption. Separate inquiry was made about the use of wine, beer, and liquor. The patients were divided into three groups on the basis of their drinking practices. Heavy drinkers were defined according to Cahalan's criteria for "high-volume high-maximum"; they consumed at least 5 or 6 drinks on some occasions and a minimum average of 1-1/2 drinks per day. In this population the heavy drinkers had a mean consumption of 4 ounces of absolute alcohol per day with 25% drinking between 8 and 16 ounces of absolute alcohol per day. The rare drinkers used alcohol less than once a month. All women who drank more than once a month but did not meet the criteria for heavy drinkers were classified as moderate drinkers. Of the first 559 women surveyed, 52 (10%) were heavy drinkers, 226 (40%) were moderate drinkers and 281 (50%) were rare drinkers.

The results so far obtained confirmed that heavy drinking is associated with heavy smoking. Sixty percent of the heavy drinkers smoked a pack or more a day in contrast to 15% of the rare drinkers.

Eleven percent of the total population reporting using psychoactive drugs at some point in their lives. In the heavy drinking group, 35% had earlier experience with barbituates, amphetamines, heroin or hallucinogens. Almost all of the patients who had used drugs had switched to alcohol before they became pregnant.

The results indicated that women classified as heavy drinkers, as contrasted with moderate and rare drinkers, have a significantly higher chance of bearing abnormal children. Their infants are at a higher risk for congenital anomalies, growth abnormalities and functional disturbances. The complete FAS has not been observed in any of these infants and no specific pattern of anomalies has been found. Four of the 37 infants (11%) born to heavy drinking women were microcephalic as compared with 1 of 245 (0.4%) in the other two groups. However, as Streissguth points out "Unfortunately other risk factors that were also significantly related to maternal drinking in this sample (smoking, maternal age and parity) were not controlled for in the statistical analyses of the outcome variables." (39) Preliminary intervention attempts among 42 heavy drinking women indicated that the 15 women who reported they abstained or significantly decreased their alcohol intake had healthier offspring than the mothers who continued as heavy drinkers during pregnancy.

Loma Linda University Study - At the 1977 Fetal Alcohol Syndrome Workshop (San Diego, California), this large prospective study being conducted at Loma Linda University in Southern California reported preliminary descriptive findings on 5,878 women attending the prenatal clinics of four hospitals (40). This study group is representative of the ethnic distribution of the general population of Southern California. Only 2.1% of this study population were classified as heavy drinkers (> 1.0 oz. absolute alcohol/ day). The report focused primarily on the characteristics

of the mothers since analysis of the findings among their infants is still in progress.

A woman who drinks heavily during pregnancy shows a characteristic profile. She is likely to be an older (>35 years) unmarried woman from the white, Hispanic or Indian group who has had previous abortions. She tends to be a smoker and have a high caffeine, sugar, and refined food intake. She is more likely to have used hard drugs and to have had binge drinking episodes. Smoking was found to be an important confounding variable. Heavy drinking women tend to be heavier smokers.

The University of Washington Study - The University of Washington prospective study was initiated in October 1974. A sample of 1,529 unselected, predominantly middle class, pregnant women receiving prenatal care at two large Seattle hospitals was interviewed in their homes during their fifth month of pregnancy regarding the quantity and frequency of alcohol consumed, diet, smoking, drugs and medications taken during and prior to pregnancy. Eighty percent of the sample drank in the month prior to pregnancy, and eighty-one percent of the sample drank during the first five months of pregnancy. Women whose average daily consumption exceeded 1.0 ounce of absolute alcohol were identified as "heavy" drinkers. 7.2% of the sample drank at that level prior to pregnancy and 2.4% continued during pregnancy. During pregnancy, 22% of the heavy drinkers were also heavy smokers, and 5% of the heavy somers were also heavy drinkers.

In various portions of the study, different subsamples of the 1,529 women were studied. The first subsample (21) consisted of

82 women who had been identified as consuming 1.0 ounces or more of absolute alcohol per day in the month prior to and/or during the first months of pregnancy, and had delivered their infants. These infants were paired with control infants randomly selected from among the offspring of light drinking and abstaining study mothers born the same day at the same hospital. Each pair of infants was referred for clinical evaluation without knowledge of maternal drinking history. Of 163 infants examined, 11 were judged as showing clinical signs of a possible prenatal effect of alcohol on growth and morphogenesis (Table 4).

Table 4

Characteristics of Infants Classified as Abnormal (21)

Case #	Clinical Features*				Average Maternal Alcohol Intake (oz/day)	
	Small Size	Micro-cephaly	Short Palpebral Fissures	FAS Dysmorphic Features (≥2)	Month Prior to Recognition of Pregnancy	First 5 months of Pregnancy
1**	±	+	+	+	25.8	1.2
2**	±	+	+	+	5.4	8.6
3	+	+	+	-	6.7	0.1
4	±	-	+	+	1.9	0.9
5	+	N.A.	N.A.	+	1.8	0.6
6	+	-	+	-	1.8	<0.1
7	+	+	+	-	1.4	0.1
8	-	+	+	+	1.4	0.7
9	-	+	+	-	1.0	1.2
10	±	-	+	±	0.0	0.0
11	±	-	+	+	0.0	0.0

*small size = weigh/or length <3rd % for sex and gestational age; microcephaly = head circumference <3rd % for sex and gestational age; short palpebral fissures = width < 1.8 cm. at gestational ages ≥36 weeks. **infants with fetal alcohol syndrome. +=abnormality present, -= abnormality absent, ± = borderline abnormality (measurement at 3rd %). N.A. = data not available or norms not applicable.

Nine of these 11 had mothers with AA*$\geq$1.0 oz. Only two of these infants were classified as having the fetal alcohol syndrome, and both of their mothers were chronic alcoholics (AA$\geq$5.0 oz. pre-recognition of pregnancy). The other seven infants, who showed lesser alterations of growth and morphogenesis "suggestive" of fetal alcohol syndrome, were born to women who reported drinking an average of 1.0 to 6.7 ounces of absolute alcohol per day in the month before recognition of pregnancy.

However, the same mothers reported much lower alcohol consumption during the first five months of pregnancy (AA between$<$0.1 to 1.2 oz. per day). Two of the eleven patients who delivered babies with features suggestive of FAS reported no alcohol consumption in the month prior to the recognition of pregnancy and during the first five months of gestation.

In examining these data, it is difficult to evaluate the role played by maternal alcohol consumption. In reporting two additional cases of FAS, this interesting paper confirms that chronic alcoholism in the mother is associated with abnormal newborns. However, it is inconclusive as far as the toxicity of "moderate" doses of alcohol consumption is concerned.

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*(AA = Average Absolute Alcohol Consumption per day; see Section B-3 for methodology and definitions.)

The sample size is small and some of the parameters measured (e.g., birth weight and length) are known to be influenced by a variety of other environmental, medical and obstetrical confounding factors not well controlled for in this study. The statistical significance of the results have been calculated by including in the "moderate-heavy" drinkers (AA $\geq$ 1.0 ounce/day) two mothers who were definitely chronic alcoholics and had children with the full-blown FAS. The large difference reported in alcohol consumption between the month prior to recognition of pregnancy and during the first five months of gestation may not be reliable. As has been pointed out (41), the difficulty lies primarily in reliance on a single, retrospective interview assessment of a woman's drinking history, and is exacerbated by the general tendency of respondents to under estimate consumption (33); it is particularly true that heavy drinkers tend to hide or underestimate alcoholic consumption.

In a second subsample, 500 neonates of interviewed mothers were examined using the Brazelton Behavioral Scale (42). Two hundred and fifty were offspring of the heaviest drinking women, and 250 were randomly selected from the non-drinkers

after feeding. The woman's estimate of her 1-month pre-pregnancy alcohol consumption was predictive of the infant's performance deficit, whereas her estimate of her alcohol consumption during pregnancy was not predictive. Maternal alcohol and nicotine consumption in combination resulted in poor neonatal performance on day 2 of life.

The authors themselves emphasized that these results should be taken with caution since, at present time, there is no evidence that performance during the neonatal period is in any way predictive of later learning ability.

Section A-3, a: STUDIES IN LABORATORY ANIMALS

Many investigations of the toxic effects of ethanol on prenatal development in animals have been performed with somewhat contradictory results (for recent reviews see 3, 50, 51).

Sandor and Elias (50) studied the effects of ethanol in chick embryos. Early maldevelopment and mortality occurred in a considerable portion of the embryos and the remaining subjects showed a significantly reduced body weight toward the end of incubation.

Ethanol exerts a variety of toxic effects of reproduction in eutherian mammals. For example, Badr et al. (52) found that alcohol is mutagenic in the mouse dominant lethal test, exerting the most marked effects against epididymal spermatozoa and late spermatids.

Ethyl alcohol has also been shown to affect fertilization and early embryonic development in the golden hamster (60). In this species the dynamics of the ova's passage along the tube after ovulation is modified by ethanol, so that normal fertilization is disturbed and polyspermia and zygote death follow.

Sandor and Amels (53) investigated the effects of ethanol on the intra-uterine development of albino rats. Ethanol (1.5 grams per kg and 2 gms per kg; i.v.) was given at six, seven and eight days of gestation in one group, and at six and seven days of gestation in another group. Ethanol, at 2 gms per kg body weight, induced twice the number of malformations than were found at 1.5 gms per kg. Skeletal abnormalities of the extremities and facial areas were recorded.

Skosyreva (54) administered daily 5 ml of 40% alcohol per kg of body weight orally to rats on days 8 to 14 of gestation. Intra-uterine mortality was 25% in the alcohol-treated animals versus 2% in the controls. There was an increased resorption rate and decreased mean fetal birth weight, but no gross skeletal or organic anomalies were noted.

Tze and Lee (55) fed female rats water containing ethanol at 30 grams per 100 ml as their only available fluid, in a balanced powdered diet. After one month, their blood alcohol concentration was 61 $\pm$ 23 mg%. A pair-fed group received a 150-calorie diet lacking ethanol. An additional control group had food and water available at all times. All three groups delivered at 21-22 days. Only 50% of the ethanol-fed mothers known to have copulated

delivered litters, and their average litter size was significantly lower than the mean litter size of eight pair-fed or control mothers. Some offspring of the alcohol fed mothers exhibited microcephaly; cracked, dry, loose skin; reddened areas on the head and body; and a generally shriveled appearance.

Kronick (56) injected pregnant mice interperitoneally with a 25% solution of ethanol in saline at a dosage of 0.03 ml per gm of body weight during different periods of organogenesis. Fetal mortality rate was substantially increased following alcohol treatment on gestation days 9 through 12. The incidence of fetal anomalies was significantly increased following alcohol treatment only on days 8, 9, and 10. Coloboma of the iris was most frequently observed in animals injected on days 8 and 9; absence of the forepaw was seen only in offspring of mothers injected on day 10. Critical periods for other anomalies were not apparent.

Chernoff (57) administered alcohol orally via an all-liquid diet (Metrecal plus ethanol, containing 15-35% ethanol-derived calories) to two highly inbred strains of mice (CBA and C3H) which differed in ethanol preference, alcohol dehydrogenase activity, and ethanol sleep time.

These diets, which resulted in alcohol blood levels of 73-398 mg/100 ml in non-pregnant females, were the sole sustenance for the females for at least 30 days before and throughout gestation. A pattern of malformations similar to those observed in human children with the fetal alcohol syndrome was noted in this study. Prenatal death and maldevelopment increased with the level of alcohol intake. At low ethanol levels, deficient occiput ossification, neural anomalies, and decreased fetal weight occurred; cardiac and eyelid dysmorphology were found in fetuses exposed to higher ethanol levels. The pattern of malformations, which was characterized by a dose-response effect and strain differences in susceptibility, indicates that chronic maternal alcoholism is embryolethal and teratogenic in mice.

Similar results were obtained by Randall et al. (58) who administered ethanol on days 5 and 10 of gestation to C57BL/6 mice as part of a nutritionally balanced diet. Twice as many fetuses were resorbed in the alcohol-fed group than in the control groups. Experimental animals had at least 1 malformed fetus per litter, while malformed fetuses were evident in only 5 of 29 control litters. While certain experimental pups had multiple anomalies, no more than 1 anomaly was noted in any affected control fetus. The experimental fetuses weighed significantly less

than controls, and had a significantly higher incidence of skeletal, heart, and abdominal/urogenital anomalies. The results of this study clearly demonstrate the teratogenicity of ethanol in C57BL/6J mice, and add empirical support to the suggestion that ethanol is the direct teratogenic agent in alcoholic beverages.

Ellis and Pick (59) have reported efforts to develop an experimental model of the fetal alcohol syndrome in the beagle. A high dose group received 5.3 gms per kg of ethanol, which is equivalent to the daily consumption of about 24 ounces of 100 proof distilled beverage (12.2 ounces of absolute alcohol) by a person weighing 135 pounds. The moderate dose group received 4.5 gms per kg (9.5 ounces of alcohol per 135 pound woman), and a low dose group received 3.0 gms per kg (6.3 ounces per 135 pound woman). The high dose of ethanol induced severe physical dependence in the pregnant beagles and completely suppressed intrauterine tissue differentiation and development of the fertilized and implanted ovum. The moderate dose produced dependence of a milder degree and permitted a more advanced intrauterine development with spontaneous abortion at 6-7 weeks gestation, or in retention within the uterus of abnormal dead fetuses. A low dose produced no detectable dependence and was followed by the birth of normal pups at term.

As far as the behavioral effects of intrauterine exposure to ethanol are concerned, Yanai et al. (61) reported that ethanol treatment of pregnant mice had little or no effect on agnostic behavior of their offspring. However, they found that ethanol administered transplacentally significantly increased the cricket-predation behavior of DBA/1BG offspring, but not that of offspring of the less predatory C57BL/10BG strain.

Similarly Elis et al. (62) found that alcohol given to pregnant mice throughout gestation resulted in more aggressive male offspring with more locomotor activity and markedly lower concentrations of 5-hydroxytryptamine in the brain. No differences between experimental and control (receiving the same volume of water) animals were noted with regard to either sociability or timidity, or in duration of gestation, number of litters, or body weight.

Yanai et al. (63) also showed in two inbred strains of mice (C57 and DBA) that the offspring of parents fed alcohol were more susceptible to audiogenic seizures and had shorter latency to seizure than either pair-fed or normally fed controls. Hyperactivity, small size with unimpaired growth rate and slow maturation of the righting reflex was observed in kittens born to mothers receiving alcohol during the last 2 weeks of pregnancy (63).

Elton et al. (64) have recently reported the results of some experiments in monkeys. Three of 4 ethanol-habituated pregnant pigtailed macaques voluntarily reduced their consumption of ethanol at conception and increased their consumption after delivery of apparently normal neonates. The offspring of the 4th monkey, whose intake averaged 5.64 g/kg daily from preconception through delivery, was assessed at birth as tremulous, overreactive, and hyperactive.

Similar results were obtained in the rat also. Bond et al. (65, 66, 67) found that prenatal ethanol administration leads to an increase in open-field activity of offspring prior to puberty and that these animals display shock-avoidance learning deficits when tested as adults.

Increased spontaneous locomotor activity in rats treated prenatally with ethanol was observed by Branchey et al. (68), who also reported increased brain tyrosine hydroxylase activity in these animals. Malakhovskii et al. (69) gave male and female white rats a 15 percent alcohol solution as the only drinking fluid for 3 months; the rats were then mated with control rats 24 hours after alcohol withdrawal. The progeny of the "alcoholized" and control animals were tested at the age of 1 month for a series of behavioral parameters. The frequency of passive and aggressive responses, the speed of acquisition of the

conditioned defense reflex, and of choosing a correct escape route were all 2 to 3 times lower in the offspring of "alcoholized" parents than in the controls. Alcoholization of the mother had a slightly stronger effect than that of the father. Microscopy did not reveal any changes in brain structure.

However, Druse et al. (70) reported CNS myelin abnormalities in rats born to mothers fed ethanol chronically for 1 month prior to conception and during gestation. The ethanol exposed pups showed elevated synthesis of myelin (particularly heavy myelin) at 18 and 25 days and decreased synthesis of all myelin subfractions (heavy, medium, and light) at 54 days. They also demonstrated increased incorporation of (3H)-leucine and (14C)-glucose into the myelin subfractions at 18 and 25 days and decreased incorporation at 54 days. Although the quantity and rate of synthesis of individual myelin subfractions was abnormal in the ethanol treated pups, the protein composition of the separated subfractions was normal. Similar findings have been reported by Rosman and Malone (71).

Martin et al. (72) also reported results on the toxic effects of ethanol in the pregnant rat. Chronic ethanol consumption by gravid rats produced certain maternal

changes as well as changes in the survival, development, and operant performance of offspring. Differences between ethanol and control groups were found for both maternal weight gain and length of gestation, while differences specific to the offspring included: number of neonatal deaths; growth retardation to postnatal day 72; date of eye opening; distance tranversed on day 15; contingent performance in the first week on continuous reinforcement, fixed ratio, and timing appetitive schedules; and number of shock initiations and ability to discriminate contingencies on punishment schedules. No gross abnormalities were observed in the major organs of ethanol-fed animals at necropsy. Possible mechanisms of the various effects were discussed.

Rawat (73) studied the effect of maternal ethanol consumption on fetal hepatic metabolism in the rat. The first measurable changes were observed after 13 days of pregnancy, when there was a steady linear increase in hepatic cytoplasmic and mitochondrial NADH reductase activity in ethanol exposed fetuses; adult levels were reached 12 days after birth.

Kesaniemi (74, 75) found that the elimination of ethanol was equal in pregnant and non-pregnant rats, but that the acetaldehyde content of peripheral blood after ethanol administration was higher in pregnant than in non-pregnant

animals. Since no differences were found in the liver alcohol and acetaldehyde dehydrogenases, a difference in the extrahepatic metabolish of acetaldehyde was suggested.

Sze et al. (76) found that mice exposed to ethanol in utero showed increased alcohol dehydrogenase activity as well as an increase in hepatic microsomal mixed function oxidase activity.

Henderson and Schenker (77) investigated the effects of maternal alcohol ingestion on fetal brain, as well as on heart, liver and kidney in rat. An all-liquid diet was employed in both the experimental animals (containing 6% w/v ethanol) and pair-fed controls. The chronic oral intake of alcohol resulted in a maternal blood alcohol concentration of 67 mg per 100 ml. The authors noted a significant increase in mortality (30%) and a decrease in body weight of alcohol-exposed pups compared to pair-fed controls. Protein concentration was unchaged in heart, liver and kidneys, but was slightly elevated in brain of the 3 day-old animals exposed to ethanol in utero. DNA synthesis rates were normal in all four organs, but DNA concentration was significantly lower in the liver of the alcohol-exposed group. In the alcohol group the total RNA levels were significantly depressed by about 10-30 percent ($p < 0.05$) in all four organs studied.

In related studies, Rawat (78) observed the effects

of long-term ethanol consumption by pregnant rats on the incorporation of 14C-leucine into ribosomal protein of fetal and neonatal brain. Fetal cerebral ribosomes incorporated 30% less 14C-leucine than controls, and neonatal rats suckling on ethanol-fed mothers showed about a 60% decrease as compared to the control group. Rawat (80) also studied rates of protein synthesis by livers of fetal and neonatal rats exposed in utero to ethanol. Rates of incorporation of labelled leucine into hepatic proteins were significantly lower in the offspring of the ethanol fed rats compared with the control group. Maternal ethanol consumption resulted in decreases in total hepatic RNA content, hepatic RNA/DNA ratio, and ribosomal protein content of the fetal liver. The retarded growth of the offspring of alcoholic mothers could be directly related to inhibition of protein synthesis.

A variety of biochemical changes have been observed in fetuses and offspring of rats exposed to ethanol during pregnancy. Maternal ethanol consumption resulted in increased levels of γ-aminobutyric acid, but decreased the acetylcholine content of the fetal brain (79) and inhibited proteolytic and tryptophan oxidase activity in the fetal liver (80). A significant, though reversible, retardation in the maturation of adrenal catecholamine

stores (81) and elevated synaptosomal tyramine uptake (82) was noted in offspring of rats treated with ethanol during pregnancy.

Chronic ethanol ingestion by pregnant rats caused alterations in the development pattern of ornithine decarboxylase activity in the heart and brain of offspring, suggesting that ethanol interferes with fetal polyamine metabolism (83, 84).

Section A-3, b: COMMENTS

From the experiments summarized above, it is clear that ethanol exerts a variety of toxic effects on reproduction in laboratory animals. For example, ethanol produces dominant lethal effects on mouse spermatozoa (52), interferes with normal tubal function and zygote development in the hamster (60), and causes intrauterine death and/or growth retardation in the developing rat and mouse conceptus (54,56).

Moreover, in some species and under certain experimental conditions, ethanol possesses teratogenic activity. Thus, when ethanol was injected into the air space of chicken eggs at early stages of incubation, the major effects were growth retardation with generalized malformations of the central nervous system leading to increased chick mortality (50). Intravenous injection of rats with ethanol on days 6 to 8 of gestation caused increased resorption, retardation of skeletal development and some abnormalities of the central nervous system (53). Injecting mice intraperitoneally in midgestation increased the resorption rate and produced offspring with coloboma of the iris and ectrodactyly (56). The administration of ethanol in the drinking water of mice over a 10-day period in mid- to late gestation resulted in small fetuses with an increased rate of minor skeletal variants (57).

Administration of ethanol to rats by a gastric cannula on days 8 to 14 of gestation resulted in an increased resorption rate and decreased fetal body weight, but no gross skeletal or visceral abnormalities were produced (54); however, ethanol administered in a liquid diet to mice 5 to 10 of gestation produced an increased incidence of structural abnormalities in addition to embryolethality and growth retardation (58).

In general, the toxic effects of ethanol within a single experiment appear to be dose-related, but it is difficult to compare results from different experiments because of variations in ethanol dosages, routes of ethanol administration, and animal species. Although oral ethanol intake by pregnant animals during the period of organogenesis has produced abnormalities in offspring (58), this has not been a constant finding (54). This could be related to the varying modalities of ethanol administration leading to variations in the level and duration of ethanol exposure of the developing embryo. For example, significant congenital abnormalities were not observed in the experiments of Skosyreva (54), who administered single daily oral doses of ethanol (5 ml of 40% ethanol per kg body weight) to 13 rats between the 8th and 14th day of pregnancy. On the contrary, Randall et al. (58) have produced convincing results indicating that ethanol supplied as part of a liquid diet to pregnant mice during morphogenesis is significantly

teratogenic. In examining these results, one is tempted to hypothesize that the embryo's duration of alcohol exposure may be an important factor in determining the teratogenicity of this compound. Thus, when given in single daily doses high levels of alcohol may be attained, but only for a relatively short time, since ethanol is rapidly metabolized. In experiments in which ethanol is incorporated in a liquid diet, toxicologically important blood levels of ethanol are likely to be maintained throughout most of the day. As will be discussed later in Section B-2, it is not known whether peak blood levels are more important in producing teratogenic effects than is the duration of embryonic exposure to a given chemical. In the case of ethanol, this issue is extremely critical, since the compound has a relatively short half-life due to its rapid metabolic degradation.

It may very well be that an occasional high level of alcohol is not sufficient to produce significant toxic effects on the developing conceptus, and that significant teratogenic effects can be obtained only with persistent toxicologically effective levels of ethanol during morphogenesis. In my opinion, this hypothesis bears an important relationship to the possible teratogenicity of "binge" drinking, and it should be actively investigated.

Furthermore, it is likely that threshold values for ethanol teratogenicity vary depending upon the route of administration and the animal species considered. Although a dose-effect relationship has been demonstrated in some experiments, in none has a threshold value for the embryolethality, growth-retarding effects and teratogenicity of ethanol been firmly established, nor has an animal experiment clearly defined the most sensitive period of gestation for ethanol toxicity.

The well-performed experiments of Chernoff (57) are intriguing in this regard, since he obtained significant teratogenic effects in two strains of rats which had been made chronically alcoholic for at least one month prior to pregnancy. These experiments in animals, as well as the human experience, raise the possibility that the development of a significant degree of tolerance to ethanol, as in a chronic alcoholic mother, may be an important contributing factor in the teratogenicity of ethanol. In these cases, whether the fetus is exposed to higher or more frequent peak levels of ethanol because of the maternal alcohol tolerance remains to be assessed. The results of Randall et al., (58) however, indicate that at least in the mouse, this is not an essential feature of ethanol teratogenicity, since congenital abnormalities were produced by an ethanol-containing liquid diet given only during the period of organogenesis.

The results obtained in experiments measuring the effects of ethanol during pregnancy on behavioral and biochemical parameters in the offspring are also difficult to interpret. There are many inconsistencies in regard to the effects of ethanol during pregnancy on the behavior of offspring (85), but this is understandable in view of the fact that in different experiments different end-points were measured in the offspring; different doses of ethanol were used at different stages of pregnancy, and different strains and animal species were used. Finally, an extrapolation of the results to the human is difficult if not impossible; as will be discussed in more detail in Section B-2, results obtained in animals on the toxicity of chemicals during pregnancy are not fully predictive for the human.

Section A-4: SUMMARY

In section A the medical and scientific evidence as to the toxic effects of alcoholic beverages and ethanol consumption during pregnancy in the human and in laboratory animals is reviewed and a few comments made.

The evidence points to a possible cause-effect relationship between abuse of alcoholic beverages during pregnancy and toxicity to the unborn child. Such a relationship is clearer when the level of alcohol consumption by the mother represents an easily recognizable chronic alcoholic condition. Thus, most of the cases of full-blown FAS have been reported in offspring of mothers who had been chronic alcoholics for a significant period of time. However, at the present time, it is less clear whether lower maternal doses of ethanol are also associated with toxic effects on the progeny, and whether other associated high risk conditions that are likely to occur in the drinking mother contribute to the toxicity of ethanol. It is also not known during which period of gestation the conceptus is most sensitive to the embryotoxic effects of ethanol exposure and whether a definite dose-effect relationship exists.

In the following section (Section B), an attempt is made to evaluate the available data on the toxicity of alcohol during pregnancy, using known pharamcological, texicological, teratological and epidemiological principles.

SECTION B-1: PHARMACOLOGICAL AND TOXICOLOGICAL PRINCIPLES

SECTION B-1, a: PHARMACOLOGY OF ALCOHOLIC BEVERAGES

An understanding of the pharmacological properties of alcohol and alcoholic beverages is essential in order to evaluate the effects of alcohol consumption during pregnancy and its possible damage to the unborn child.

An outline of the most important aspects of the pharmacology of alcohol and alcoholic beverages is given below. For a comprehensive review of this subject, the reader is referred to a series of excellent reviews (86, 87, 88, 89, 90, 91).

Pharmacokinetics of Ethanol

Ethyl alcohol, or ethanol, is the pharmacologically active ingredient in beer, wine, whiskey, gin, brandy, and other less common alcoholic beverages. In addition to ethanol, alcoholic beverages contain a variety of other chemicals, but as far as we know they have no important pharmacologic properties. A comprehensive review of the chemical composition of alcoholic beverages has recently been published (92).

Ethanol is absorbed from both the stomach and the small intestine. Its presence may be detected in the blood within 5 minutes after ingestion, and the maximum concentration is reached in 30 to 90 minutes. The ingestion of milk and fatty foods impedes, and water facilitates, its absorption.

There is no indication that high-alcohol beverages are more toxic than low-alcohol beverages, based on equivalent amounts of alcohol, or that they contain any peculiarly toxic component. On the other hand, there are some results indicating that following ingestion of equivalent amounts of ethanol, vodka, gin and whiskey produce higher blood levels of ethanol than beer and wine (93).

After entering the bloodstream, alcohol reaches various organs, as well as spinal fluid, urine, and pulmonary alveolar air, attaining concentrations which bear a constant relationship to those in the blood. Alcohol distributes in the total body water (TBW), and in fact, blood ethanol concentrations reflect the TBW volume. TBW in women is 45.5% of body weight, whereas it is larger (51.5%) for men. Thus, after ingesting equal amounts of ethanol, higher blood ethanol levels will be present in women than in men.

Lester (94, 95), on the basis of his own work and a review of the literature concluded that man and most mammals produce approximately 12-39 g of endogenous ethanol/24 hr. Krebs and Perkins (96) showed in rats and Blomstrand (97) in a patient that this endogenous alcohol is formed in the gut.

Alcohol is metabolized principally through oxidation by alcohol dehydrogenase (ADH), first to acetaldehyde and then to acetate, which is released into hepatic venous blood. The acetate is then metabolized mainly in peripheral tissues to acetyl coenzyme A, which enters the Krebs cycle, with eventual release of water

and carbon dioxide. Less than 10% is excreted chemically unchanged in urine, sweat and breath. These metabolic pathways are well known and widely described. Although 80% or more of ingested alcohol is metabolized in the liver, small amounts of ADH are found in the intestinal and gastric mucosa, lungs, kidney, spleen, prostate, testis, and retina; this extra-hepatic ADH activity may play a minor metabolic role, which could increase during excessive or long-continued use (98).

Alcohol is oxidized and eliminated at a fairly constant rate. The First Special Report to the U. S. Congress on Alcohol and Health (99) states "In a 150-pound man, alcohol is metabolized at approximately one drink per hour." A typical drink is defined as one containing 3/4 oz. (17.5 g) of ethanol, the amount in 1.9 oz. of 80-proof spirits. If, therefore, a man weighing 70 kg (154 lbs.) drank this amount every hour and there was prompt absorption, the blood alcohol level should theoretically be zero at the end of each hour.

That pattern of drinking, of course, bears little resemblance to what happens in real life. Studies in man by Mezey and Tobon (100) have shown that the average metabolism is about .15 g/kg/hr, or 252 g in 24 hours in a 70 kg man. Newman et al. (101, 102), on the basis of limited studies in dogs and humans, concluded that the maximal amount of alcohol that can ordinarily be metabolized is about 300 g per day. Beerstecher (103) and Rohan (104) cite instances, however, in which actual daily intake has exceeded this amount for months or years.

Blood alcohol levels reflect the amount ingested, absorption from the gut, distribution in body water and metabolism. Early studies (105) showed that after rapid ingestion of 22 g ethanol in the form of undiluted whiskey or a martini on an empty stomach, the blood level rises to about 45 mg/100 ml in about 30 minutes, then begins to fall, becoming undetectable at 3 hours. After ingestion of 44 g in the same form, blood levels reach about 80 mg/100 ml in 30-45 minutes, then fall steadily but are usually detectable for 6 hours, with small amounts remaining in the stomach during most of this period.

There is considerable individual variation, due mainly to unequal absorption from the stomach. Mellanby (106), using dogs, and Haggard et al. (107), employing human subjects, found that when the same amount of alcohol is diluted or taken with or after a meal, blood levels reached are not as high, probably owing to slower absorption; elimination, however, occurs at about the same rate. The essential validity of these observations has been confirmed by many workers. Within wide ranges, therefore, blood levels can be related to type of intake and time. However, intake and blood levels are more difficult to correlate consistently with acute effects.

The phenomenon of tolerance to alcohol is not well understood, although it is an important element in the body's reaction to alcohol and may be a key factor in permitting the daily ingestion of very large amounts without apparent harm for many years. The linkage of tolerance to physical dependence and its attendant withdrawal syndrome is likewise not well understood.

Very few factors are capable of increasing the rate of alcohol metabolism. However, it seems well established that

chronic alcoholics metabolize alcohol faster than normal individuals. Amino acids (especially alanine) and fructose also enhance ethanol metabolism, but their clinical utility is limited. Alcohol also reduces the intestinal absorption of nutrients such as glucose, amino acids, calcium, folate, and vitamin B_{12}. This inhibition of absorption may contribute to the malnutrition frequently found in alcoholic subjects. Starvation slows the rate of alcohol metabolism in the liver, although this varies greatly in degree from one person to another.

Pharmacological Effects of Ethanol (108)

Cardiovascular System. There appears to be a direct action of alcohol on the excitability and contractility of heart muscle. With intoxicating doses there is a rise in cardiac rate and output and in systolic and pulse pressures, and a cutaneous vasodilatation at the expense of splanchnic constriction. Some authors have stated that prolonged intoxication may have a damaging effect on cardiac and skeletal muscle, a degeneration of fibers supposedly due to suppression of myophosphorylase activity. Increased sweating and vasodilatation cause a loss of body heat and a fall in body temperature.

Stomach. In low concentration (<10%) by whatever route it is administered, alcohol stimulates the gastric glands to produce acid, apparently by antral activation of gastrin release, and possibly by causing the tissues to form or release histamine. With the ingestion of alcohol in concentrations of over 10 to 15 percent, the secretion of mucus is increased, the stomach

mucosa becomes congested and hyperemic, and the secretion of acid may then become depressed. This is a state of acute gastritis, from which recovery may be relatively rapid. The increase in appetite following ingestion of alcohol is due to the stimulation of the end organs of taste and to a general sense of well-being.

Metabolic Effects. Alcohol has a number of metabolic effects. In the area of lipid metabolism it can cause hypertriglyceridemia as well as lead to a fatty liver. It interferes with carbohydrate metabolism and can produce hypoglycemia by impairing gluconeogenesis; however, a significant degree of hypoglycemia will occur only if hepatic glycogen stores are depleted. Under certain conditions, alcohol can also interfere with the peripheral utilization of glucose and produce hyperglycemia. When ethanol is oxidized, there is a simultaneous generation of reduced nicotinamide adenine dinucleotide; as a result pyruvate is converted to lactate. Thus alcoholism may result in increased levels of serum lactate, occasionally lactic acidosis and also hyperuricemia secondary to the inhibitory action of lactic acid in the renal excretion of uric acid.

Renal System. Alcohol drinkers frequently exhibit low serum levels of phosphate and magnesium presumably because of increased renal excretion of these ions. There are also well-recognized effects on water excretion. The ingestion of 4 oz. of 100-proof bourbon whiskey may result in a diuresis comparable to that which follows the drinking of large amounts of water.

This diuresis is most likely due to the transient suppression of the release of antidiuretic hormone from the supraopticohypophyseal system. However, diuresis occurs only during the initial phase of alcohol administration and does not persist during prolonged drinking. There is also increased urinary excretion of ammonium and a titratable metabolic and respiratory acidosis. The former is presumably due to an accumulation of acid metabolites and the latter to the direct action of alcohol on the respiratory center.

Nervous System. It is now generally accepted that alcohol is not a central nervous system (CNS) stimulant, but a depressant. Some of the early and apparent stimulatory effects of alcohol, manifested as garrulousness, agressiveness, excessive activity, and increased electrical excitability of the cerebral cortex, are due to the inhibition of certain subcortical structures (high brainstem reticular formation) which ordinarily modulate cerebral cortical activity. Similarly, the initial hyperactivity of tendon reflexes may represent a transitory escape of spinal motor neurons from higher inhibitory centers. With increasing amounts of alcohol, however, the depressant action spreads to involve the cerebral neurons as well as other brainstem and spinal neurons.

All types of motor performance, whether the simple maintenance of a standing posture, the control of speech and eye movements, or highly organized and complex motor skills, is

adversely affected by alcohol. The movements involved in these acts are not only slower than normal but also more inaccurate and random in character and therefore less adapted to the accomplishment of specific ends.

Alcohol also impairs the efficiency of mental function by interfering with the learning process, which is slowed and rendered less effective. The facility of forming association, whether of words or figures, tends to be hampered and the power of attention and concentration is reduced. The person is not as versatile as usual in directing thought along new lines appropriate to the problems at hand. Finally, alcohol impairs the faculties of judgment and discrimination and, all in all, the ability to think and reason clearly.

A scale relating the various degrees of clinical intoxication to the blood alcohol levels in nonhabituated persons has been constructed. At blood alcohol levels of 30 mg per 100 ml, a mild euphoria exists, and at 50 mg per 100 ml, a mild incoordination. At 100 mg per 100 ml, ataxia is obvious; at 300 mg per 100 ml, the patient becomes stuporous; and a level of 400 mg per 100 ml is accompanied by deep anesthesia and could prove fatal. These figures are valid, provided that the alcohol content rises steadily over a 2 hour period. It should be emphasized, however, that such a scale has no value in the chronic alcoholic. It does not take into account two adaptive changes that every organism makes to alcohol: an increased rate of alcohol metabolism by the liver and the development of tolerance.

It is common knowledge that an habituated individual can drink more alcohol and show fewer of its nervous system effects than a moderate drinker or abstainer. In the chronic alcoholic subject the ingestion of a given amount of alcohol will result in a lower blood alcohol level than in a non-alcoholic individual; furthermore, for a given blood alcohol level one will observe lesser degrees of "drunkenness" or inebriation. The organism is capable of adapting to alcohol after a very short exposure. If the alcohol concentration in the blood is raised very slowly, no symptoms appear, even at quite high levels. It would appear that the important factor in this rapid adaptability is not so much the rate of increment or the height of the blood alcohol level, but the length of time the alcohol has been present in the body. It has also been shown that if the dosage of alcohol which causes blood levels to reach a certain height is held constant, the blood alcohol concentration falls and clinical evidence of intoxication disappears. The cause of this fall in alcohol concentration is not clear. This type of tolerance has been termed "metabolic" and refers to the adjustments made by the nervous system to long-continued exposure to alcohol. There must be a subtle alteration in the metabolism of the neurons such that they can function in the face of high tissue alcohol levels. This alteration requires some time for its establishment. Removal of alcohol from the habituated nervous system results in another disturbance in neuronal function, presumably an overactivity.

Pharmacogenetics of Ethanol

Theoretically, genetic factors might influence both the metabolism of alcohol and the effects of alcohol on physiological functions. It has not yet been determined to what extent alcohol metabolism is conditioned by genetic factors. According to von Wartburg and Schürch (109), alcohol dehydrogenase, the enzyme which catalyses alcohol metabolism, occurs in two forms, a typical and an "atypical" form. The frequency of these two types was investigated in various population groups and found to vary greatly. In Sweden, the "atypical" form was present in 4%, in Switzerland in 20% and in Japan in 90-95% of the population. The significance of the difference between countries is obscure. Fenna et al. (110) observed that the rate of alcohol metabolism was more rapid in white individuals than in Indians and Eskimoes.

Similar racial differences have been found in the field of pharmacogenetics. In glycogenosis type I, i.e., an "inborn error of metabolism," the alcohol elimination rate was found to be three to four times more rapid than normal. The absence of alcohol dehydrogenase is apparently incompatible with life, since individuals lacking this enzyme have so far not been encountered. The investigation of ethnic differences in alcohol sensitivity carried out by Wolff is of special interest (111). He gave alcohol to young and adult Japanese, Taiwanese, Koreans and Caucasians and found that their responses to alcohol showed great variations: of the white children only 5%

responded with marked flushing of the face as compared with 74% of the Asian children. This also applied to adults in which great differences were also noted in their heart rates and in subjective intoxication.

Pharmacokinetics and Pharmacologic Effects of Ethanol during Pregnancy

The information on the pharmacokinetics and pharmacological effects of ethanol described above were obtained in adult males and less frequently in nonpregnant females. Whether these pharmacological effects are fully valid when applied to pregnant females remains to be assessed.

Significant physiological changes take place during the course of human pregnancy (112, 113, 114). Alternations in maternal weight and increased extra- and intracellular fluid are not dur to the growing conceptus alone, but are also attributable to profound changes in maternal physiology (Figure 1, Table 5).

TABLE 5

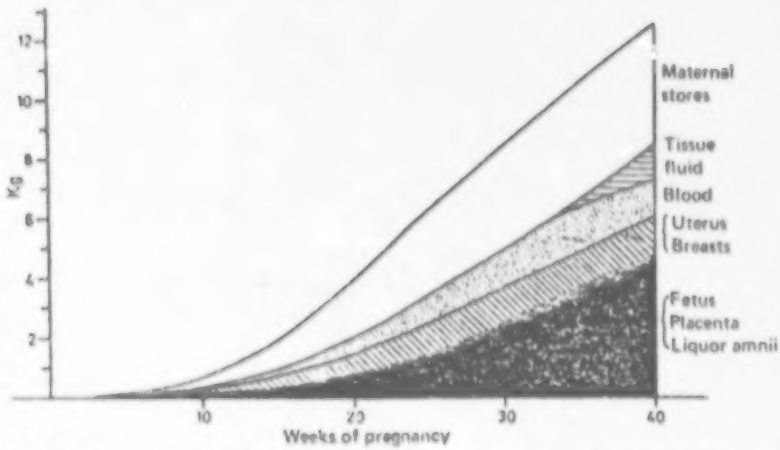

FIG. 1 Components of weight gain in normal pregnancy. (Hytten FE, Leitch I: The Physiology of Normal Pregnancy. Oxford, Blackwell, 1964)

TABLE 5. Estimate of Extracellular and Intracellular Water Added During Pregnancy

	Total water (ml)	Extracellular (ml)	Intracellular (ml)
Fetus	2343	1360	983
Placenta	540	260	280
Liquor amnii	792	792	0
Uterus	743	490	253
Mammary gland	304	148	156
Plasma	920	920	0
Red cells	163	0	163
Extracellular extravascular water	1195	1195	0
Total	7000	5165	1835

Hytten FE, Leitch I: The Physiology of Human Pregnancy. Oxford, Blackwell, 1964

Thus, the physiological adaptive mechanisms of pregnancy involve marked changes in the respiratory, cardiovascular, gastrointestinal and urinary systems of the mother as well as metabolic changes (Table 6).

Table 6: SUMMARY OF MEASURABLE PREGNANCY CHANGES

Parameter	Percent* Increase	Decrease
Respiratory System		
Tidal volume	30-40	
Resistance of tracheobronchial tree		36
Expiratory reserve		40
Residual volume		40
Functional residual capacity		25
Respiratory minute volume	40	
Cardiovascular System		
Heart rate	0-40	
Stroke volume	x	
Cardiac output	20-30	
Peripheral blood flow	600	
Blood volume	48	
Gastronintestinal System		
Cardiac sphincter tone		x
Acid secretion		x
Motility		x
Gallbladder emptying		x
Urinary Tract		
Renal plasma flow	25-50	
Glomerular filtration rate	50	
Ureter tone		x
Metabolism		
Oxygen consumption	14	

* change from non-pregnant values

These maternal changes are likely to modify the physiologic disposition of, and response to, ethanol so that the pharmacological effects of drinking equivalent amounts of alcohol may differ in pregnant versus nonpregnant females. It is unfortunate that little, if any, information is available on this subject.

SECTION B-1, b: CLINICAL MANIFESTATIONS OF ALCOHOLISM (115)

Although alcohol may alter the function of practically every organ system, the most important clinical effects are on the digestive organs and on the nervous system.

Effect on the Digestive Organs

Gastritis. Morning nausea and vomiting are symptoms common in alcoholics. Characteristically, the patient can suppress these symptoms by taking a drink or two, after which he is able to consume large quantities of alcohol without the recurrence of the symptoms until the following morning.

Other complaints referable to the gastrointestinal system are abdominal distention, epigastric distress, belching, typical or atypical ulcer symptoms, and hematemesis. The most common pathologic basis for these symptoms is a superficial gastritis, which is an almost invariable sequel to prolonged drinking. Most instances of gastritis are benign, and the symptoms subside after a few days of abstinence, but more severe forms are associated with mucosal erosions or ulcerations and may be the source of serious bleeding. The incidence of peptic ulcer is exceptionally high in alcoholics. A less frequent but serious cause of hematemesis is the so-called Mallory-Weiss syndrome,

which is characterized by lacerations of the mucosa at or just below the gastroesophageal junction.

Hepatitis. Patients admitted to the hospital following a period of prolonged drinking and severe dietary depletion almost invariably show enlargement of the liver because of infiltration of the parenchymal cells with fat. This fatty liver is essentially reversible provided that the patient remains abstinent and receives a nutritious diet. A form of hepatocellular necrosis or alcoholic hepatitis is observed frequently in chronic alcoholics, especially following a severe drinking bout. About 8 percent of patients with severe alcoholism develop a permanent form of liver disease, i.e., cirrhosis, in which a diffuse proliferation of fibrous tissue replaces the normal lobular architecture of the organ.

Pancreatitis. The excessive use of alcohol is also a significant factor in the causation of pancreatitis. The mildest form of this disorder may be attributed to gastritis or may go unnoticed. In more severe form, pancreatitis presents as an acute abdominal catastrophe, i.e., with epigastric pain, vomiting, and rigidity of the upper abdominal muscles. In these circumstances the pancreas appears tense and edematous, often with a serosanguinous exudation of fluid on its surface. The most severe form is that of hemorrhagic pancreatitis. Alcoholics may also develop a chronic relapsing form of pancreatitis, often associated with irregular calcification of the pancreas.

Effect on the Nervous System

A large number of neurologic disorders are associated with alcoholism, as listed in Table 7. The factor common to all of them is the abuse of alcohol, but the mechanism by which alcohol produces its effects varies widely from one group of disorders to another.

Table 7

NEUROLOGIC DISORDERS ASSOCIATED WITH ALCOHOLISM

I. Alcohol intoxication - drunkenness, coma, excitement ("pathologic intoxication")

II. The abstinence or withdrawal syndrome - tremulousness, hallucinosis, "rum fits," delirium tremens

III. Nutritional diseases of the nervous system secondary to alcoholism
   A. Wernicke - Korsakoff syndrome
   B. Polyneuropathy
   C. Optic neuropathy ("tobacco-alcohol amblyopia")
   D. Pellagra

IV. Diseases of uncertain pathogenesis associated with alcoholism
   A. Cerebellar degeneration
   B. Marchiafava-Bignami disease
   C. Central pontine myelinolysis
   D. Cerebral atrophy
   E. "Alcoholic" cardiomyopathy and myopathy

V. Neurologic disorders consequent upon Laennec's cirrhosis and portal-systemic shunts
   A. Hepatic stupor and coma
   B. Chronic hepatocerebral degeneration

I. Alcohol Intoxication. The signs of drunkenness consist of varying degrees of exhilaration and excitement, loss of restraint, irregularity of behavior, loquacity, slurred speech, incoordination of movement and gait, irritability, drowsiness, and, in advanced cases, stupor and coma. On rare occasions acute intoxication is characterized by an outburst of irrational, combative and destructive behavior, which terminates when the patient falls into a deep stupor and for which he may later have no memory. This state has been referred to as "pathologic intoxication" or "acute alcoholic paranoid state." Allegedly this reaction may follow the ingestion of relatively small amounts of alcohol, and it has been variously ascribed to constitutional differences in susceptibility to alcohol, previous cerebral injury, and "an underlying epileptic predisposition." However, there are no critical data to support any of these contentions.

Alcohol acts on nerve cells in a manner akin to the general anesthetics. Unlike the latter, however, the margin between the dose of alcohol that produces surgical anesthesia and that which dangerously depresses respiration is a very narrow one, a fact which accounts for the occasional fatality in cases of alcoholic narcosis. Alcoholic coma is characterized by serious depression of respiration, heralded by a loss of corneal and pupileary reflexes. In fatal cases periperal vascular collapse preceeds death.

II. The Abstinence or Withdrawal Syndrome. A second category of alcoholic neurologic disease comprises the tremulous, hallucinatory, epileptic, and delirious states. Although a sustained period of chronic intoxication is the underlying factor in each of these disorders, the symptoms become manifest only after a period of relative or absolute abstinence from alcohol - hence the designation abstinence or withdrawal syndrome. The prototype of the patients afflicted with these symptoms is the binge or periodic drinker, although the steady drinker is not immune if, for some reason, he or she stops drinking.

By far the most common manifestation of the abstinence syndrome is a state of tremulousness, commonly referred to as "the shakes" or "the jitters" combined with general irritability and gastrointestinal symptoms, particularly nausea and vomiting. The symptoms first show themselves after several days of drinking, usually in the morning, after the short period of abstinence that occurs during sleep.

Generalized tremor is an outstanding feature of this illness. It is of fast frequency (6 to 8 oscillations per second), slightly irregular, and variable in its severity, tending to diminish when the patient is in quiet surroundings and to increase with motor activity or emotional stress. The tremor may be so violent that the patient cannot stand without help, speak clearly, or feed himself.

Although the flushed facies, anorexia, tachycardia, and tremor subside to a large extent within a few days, the patient does not regain his full composure for a much longer time. The overalertness, tendency to startle easily, and jerkiness of movement may persist for a week or longer; the feeling of uneasiness may not leave the patient completely for 10 to 14 days.

Symptoms of disordered perception (hallucinosis) occur in about one-quarter of the tremulous patients. The patient may complain of "bad dreams" -- nightmarish episodes associated with disturbed sleep, which are difficult to separate from real experience. Sounds and shadows may be misinterpreted, or familiar objects may be distorted and assume unreal forms. Although these are not hallucinations in the strict sense of the term, they represent the most common forms of disordered sense perception in the alcoholic. Hallucinations may be purely visual or auditory in type, mixed visual and auditory, and occasionally tactile or olfactory. There is little evidence to support the popular belief that certain visual hallucinations are specific to alcoholism. They are more commonly animate than inanimate and may comprise various forms of human, animal, or insect life.

In this particular setting (i.e., where relative or absolute abstinence follows a period of chronic inebriation) there is a marked tendency to develop convulsive seizures (withdrawal seizures or "rum fits"). Over 90 percent of

seizures occur during the 7- to 48-hour period following the cessation of drinking, with a peak incidence between 13 to 24 hours. During the period of seizure activity the electroencephalogram may be abnormal, but it reverts to normal in a matter of days, even though the patient may go on to develop delirium tremens. Almost one-third of the patients with generalized seizure activity go on to develop delirium tremens, in which case the seizures invariably precede the delirium.

Delirium tremens is the most dramatic and grave of all the alcoholic complications. It is characterized by profound confusion, delusions, vivid hallucinations, tremor, agitation, and sleeplessness, as well as by increased activity of the autonomic nervous system, i.e., dilated pupils, fever, tachycardia, and profuse perspiration.

Delirium tremens develops in one of several settings. The patient, an excessive and steady drinker of many years' duration, may have been admitted to the hospital for an unrelated illness, accident, or operation, and 3 to 4 days later becomes delirious. Or following a prolonged spree, he may have already experienced several days of tremulousness and hallucinosis, or one or more seizures, and may even be recovering from these symptoms, when he suddenly develops delirium tremens.

In the majority of cases delirium tremens is benign and short-lived, ending as abruptly as it begins. Consumed by the relentless activity and wakefulness of several days' duration,

the patient falls into a deep sleep; he awakens lucid, quiet, and exhausted, with virtually no memory for the events of the delirious period.

About 15 percent of cases of delirium tremens, as defined above, end fatally. In many of these there is an associated infectious illness or injury, but in a few no complicating illness is discernible. Patients frequently die in a state of hyperthermia or peripheral circulatory collapse; in some, death comes so suddenly that the nature of the terminal events cannot be determined.

III. Nutritional Diseases of the Nervous System. The Wernicke-Korsakoff syndrome, alcoholic polyneuropathy, optic neuropathy ("tobacco-alcohol amblyopia") and pellagra are considered under this heading. These diseases compose a relatively small but serious group of illnesses in chronic alcoholics. In contrast to the role of alcohol in intoxication and abstinence syndromes, its role in these nutritional diseases is purely secondary, serving mainly to displace food in the diet.

IV. Alcoholic Diseases of Uncertain Pathogenesis. Included in this category are several diverse disorders which are practically always encountered in alcoholic patients. Their relationship to the excessive use of alcohol is not fully understood and probably is not crucial, since all of them have been described in nonalcoholic patients. There is a considerable amount of indirect evidence that these disorders

are nutritional in origin, but as yet this relationship must be regarded as unproved.

Alcoholic Cerebellar Degeneration. This term is applied to a nonfamilial type of cerebellar ataxia which occurs in adult life against a background of prolonged ingestion of alcohol. The symptoms frequently evolve in a subacute fashion (several weeks or months), after which they remain stationary for many years. The signs are those of cerebellar dysfunction, affecting stance and gait predominantly. Once established, the signs change very little, although some improvement of gait (due mainly to recovery from complicating polyneuropathy) may follow cessation of drinking. The essential pathologic changes consist of degeneration of varying severity of all the neurocellular elements of the cerebellar cortex, particularly of the Purkinje cells, with a striking topographic restriction to the anterior and superior aspects of the vermis and hemispheres.

Marchiafava-Bignami Disease (Primary Degeneration of the Corpus Callosum). This is a rare complication of alcoholism. The symptoms are diverse and include pyschic and emotional disorders, delirium and intellectual deterioration, convulsive seizures, and varying degrees of tremor, rigidity, paralysis, apraxia, aphasia, and sucking and grasping reflexes. The duration is variable, from several weeks to months, and recovery is possible. The pathologic picture consists of symmetrically placed areas of demyelination in the corpus callosum, particularly the middle lamina.

Pontine Myelinolysis. This term refers to a unique pathologic change affecting the center of the basis pontis, in which the medullated fibers are destroyed in a single symmetric focus of varying size. The disease may manifest itself by pseudobulbar palsy and quadriplegia, but usually the lesion is so small that it causes no symptoms and is found only at postmortem examination. The relationship of this condition to either alcoholism or malnutrition is obscure, but most of the cases have occurred in patients with prolonged and severe nutritional depletion.

Cerebral Atrophy. The pathologic examination of relatively young alcoholic patients not infrequently discloses an unexpected degree of convoluntional atrophy, most prominent in the frontal lobes, and a symmetric enlargement of the lateral and third ventricles. The ventricular enlargement may also be found on pneumoencephalography. In some patients these findings are associated with overt complications of alcoholism, such as the Wernicke-Korsakoff syndrome, but in many of them no other abnormalities can be found, and the history discloses no symptoms of neurologic disease. The nature of this disorder is quite unclear.

"Alcoholic" Myopathy. Attention has been drawn to several disorders of skeletal and cardiac muscle, apparently primary in nature, in association with chronic alcholism. One type of myopathic syndrome, which may be generalized or focal, is characterized by the acute onset of severe pain, tenderness,

and edema of muscles, accompanied by myoglobinuria, renal damage, and hyperpotassemia in severe cases. In other cases, diffuse muscle weakness is associated with hypopotassemia and vascular necrosis of muscle. It should be noted that these acute forms of muscle weakness are not confined to alcoholics. Another type of myopathy is characterized by the subacute development of weakness and atrophy of the proximal limb and girdle muscles, with "myopathic" changes in the electromyogram and elevated creatine phosphokinase levels in serum, but without local pain or edema. Muscle power is slowly restored in these patients following abstinence from alcohol and improvement in nutrition. That this disorder represents a primary affection of muscle has not been established beyond doubt. Muscle biopsies from such patients suggest that it may represent a proximal form of polyneuropathy, despite relatively mild clinical signs of peripheral nerve disease.

"Alcoholic cardiomyopathy" is the name given to a nonspecific affection of cardiac muscle which has a higher incidence in patients with chronic alcoholism than in the non-alcoholic population. The role of alcohol, malnutrition, or some hitherto unsuspected factor in the genesis of these disorders is not known, and their structural and biochemical bases requires further study.

V. Neurologic Disorders Consequent Upon Cirrhosis and Portal-System Shunts. Hepatic coma refers to an episodic disorder of consciousness which frequently complicates (or terminates) advanced liver disease and/or portal-system shunts. It is associated with typical electroencephalographic abnormalities and intermittency of sustained muscular contraction which presents as an irregular flapping movement of the outstretched limbs (asterixis).

Less frequently, cirrhosis is complicated by a chronic and largely irreversible form of hepatocerebral disease, the main symptoms of which are dementia, dysarthria, ataxia, and athetosis. A failure to metabolize ammonium, or perhaps some other substance absorbed from the bowel, may be the result of either hepatocellular disease or of shunting of blood around the liver. Presumably, the acute and rapidly developing effect of this toxin on the brain is episodic stupor or coma, which is reflected pathologically by a diffuse astrocytic hyperplasia in the CNS; a prolongation of this effect may lead to irreversible neurologic symptoms and parenchymal lesions.

Section B-1, c: PHARMACOLOGICAL AND TOXICOLOGICAL PRINCIPLES OF ALCOHOL CONSUMPTION AND PREGNANCY OUTCOME. This brief review emphasizes that the pharmacological and medical implications of alcohol consumption are complex. The historic difficulty in clearly distinguishing the alcohol user from the alcohol abuser, and the lack of a generally accepted definition of

alcoholism (116) is an indication of this complexity.

Alcohol drinkers differ from each other in a number of respects, including amount of ethanol ingested on each occasion, pattern of drinking, length of alcohol consumption, and dependence and tolerance to alcohol. As a result of these differences, alcohol use may result in acute recurrent intoxications or in a number of chronic, some of them progressive, disorders with different degrees of social and health ramifications. Hore (117) describes two phases in drinking behavior: a) the pre-dependent phase, where drinking behavior is best understood as the result of a combination of psychological and social factors, and in which the sequelae of physical dependence are absent, and b) the dependent phase proper, with evidence of physical dependence. Since most would agree that alcoholism is defined as dependence (addiction) to alcohol, then the pre-dependent phase has been termed "normal", or "social", drinking.

Jellinek (116) however, differentiates five species of alcoholism: alpha - representing a purely psychological continued dependence without loss of control or inability to abstain; beta - that form in which physical complications occur without either physical or psychological dependence; gamma - alcoholism in which there is acquired tissue tolerance, adaptive cell metabolism, physical dependence and loss of control; delta - alcoholism with inability to abstain instead of loss of control; and episilon alcoholism (dipsomania) - which is periodic alcoholism.

These classifications and the disease concept of alcoholism have been the subject of much debate (118), clearly pointing out that "alcoholics" are an ill-defined group which is difficult to identify. Furthermore, since they may differ in a number of respects from each other, they are an heterogeneous population and therefore difficult to characterize. Except for extreme cases of chronic alcoholism, the alcoholic (alcohol addict) can hardly be differentiated from the "social drinker" (non-alcohol addict). The alcoholic is rarely identified by physicians or other health or law officials before the disease becomes a significant medical or social problem (117).

In examining the pregnancy outcome of women using (or abusing) alcoholic beverages, careful consideration should be given to the multiple pharmacological, toxicological, medical and social implications of alcohol use.

This problem has been considered and attempts have been made to better characterize alcohol drinking mothers with poor pregnancy outcome. For example, Jones et al. (2), in reporting 8 cases of FAS in children of chronic alcoholic mothers, attempted to better define the degree of maternal alcoholism by examining the duration of maternal alcoholism and the presence or absence of delirium tremens, cirrhosis and nutritional anemia (Table 8).

TABLE 8: Maternal History of Alcoholism in Eight Mothers with FAS Children (2)

History of alcoholism	Patient Number								All cases
	1	2	3	4	5	6	7	8	
Duration (years)	7	3	4	11	2+	10	23	15	9.4*
Delirium tremens	+	?	+	+	?	-	+	+	5/6
Cirrhosis	-	?	-	+	?	-	+	-	2/6
Nutritional anemia	-	?	-	+	?	-	+	-	2/6

*Mean + = present; - = absent; ? - unknown

The clear delineation of the degree of duration of maternal alcoholism may be very important in assessing the role played by alcohol in the FAS. This may be particularly true in assessing the possible teratogenicity of "low" doses of ethanol. Thus, from a pharmacological and toxicological point of view, the effects of drinking 2 or 3 ounces of absolute alcohol per day markedly differs, depending upon the number of doses (drinks) in which this amount is administered during the day, the type of alcoholic beverage used, the degree of maternal alcohol tolerance, and whether this amount of alcohol is ingested during meals or on an empty stomach. As pointed out by Streissguth (119), the identification and detailed description of the drinking woman are important aspects of any study involving drinking habits in the mothers and pregnancy outcome.

It may very well be that the method of classifying women into arbitrary groups (e.g., light, moderate, and heavy drinkers) by determining only the average daily alcohol intake will prove too insensitive for establishing a clear relationship between alcoholic beverage consumption in women and poor pregnancy outcome.

SECTION B-2: TERATOLOGIC PRINCIPLES

An evaluation of the data presented in Section A reveals that there is a relationship between alcoholic beverage consumption by the mother and poor pregnancy outcome. Although this relationship has been suspected for a long time, only recently it has been firmly established by the outstanding contributions of Lemoine et al. (1) and Jones et al. (2). It was through the efforts of these authors, working independently, that clinical detection of the toxicity of alcohol consumption was made possible, because they grouped together a series of rather aspecific birth defects into a well-defined teratologic syndrome which they termed the FAS. Listed in Table 9 are the criteria for recognizing a new teratogenic agent in man; the first criteria is an abrupt increase in the incidence (or recognition) of a particular defect or syndrome. There are now well over 200 cases of FAS reported in the literature. Since almost all the cases have been reported in offspring of chronic alcoholic women, it is clear that heavy and prolonged alcohol beverage consumption by the mother fulfills the first criterion for recognition of teratogenicity in the human. However, this criterion has not yet been met for moderate alcoholic beverage consumption, e.g., that not associated with medically recognizable signs of maternal chronic alcoholism.

Although there are still some (120) who question ethanol as the etiologic agent causing growth and behavior disorders in the offspring of female alcohol abusers, there is no doubt that ethanol remains the only common consumption factor in all reported cases of FAS (121). Thus, according

to Clarren and Smith (4), whatever the basic biochemical mechanism of FAS teratogenesis is, alcohol beverage consumption plays a key role.

Although criterion 1 of Table 9 is clearly met, criterion 2 does not really apply to ethanol, and the available clinical evidence is insufficient to draw any conclusions for criteria 3 and 4.

TABLE 9. CRITERIA FOR RECOGNIZING A NEW TERATOGENIC AGENT IN MAN (122).

1. An abrupt increase in the incidence of a particular defect or association of defects (syndrome).
2. Coincidence of this increase with a known environmental change, e.g., widespread use of a new drug.
3. Known exposure to the environmental change early in pregnancies yielding characteristically defective infants.
4. Absence of other factors common to all pregnancies yielding infants with the characteristic defect(s).

Thus, it is not known whether maternal exposure to alcohol during early pregnancy yields characteristically defective infants. It has been suggested that "binge" drinking in early pregnancy may be responsible for alcohol teratogenicity, but as far as I know, there are no human data supporting such an hypothesis. Further, it is not known whether pre-pregnancy chronic ethanol exposure with or without early (or late) pregnancy exposure is an important factor in the teratogenicity of alcohol in the human.

As far as criterion 4 is concerned, all other factors known to be associated with alcoholic women (e.g., malnutrition, drug use, cigarette smoking, etc.) must be eliminated as possible etiologic and/or contributing factors in the FAS. As will be discussed later in the epidemiology section (Section B-3), the relative importance of these associated factors is unclear, although active investigations are under way to elucidate this difficult area.

The task of evaluating the potential teratogenicity of "low" (or "moderate") doses of alcohol during pregnancy is particularly difficult. As mentioned before, the full-blown FAS is characteristic only of infants whose mothers have been alcoholic for a prolonged period (usually years) before gestation. Therefore, attempts have been made to relate alcohol consumption by the mother to other less specific end-points related to alcohol embryotoxicity including stillbirth, decreased birth weight, prematurity, neonatal survival, and congenital malformations. No clear conclusions have as yet emerged.

An intrinsic difficulty of these studies is that all the commonly measured signs of poor pregnancy outcome are aspecific and known to have a multifactorial etiology (112). As far as FAS is concerned, Clarren and Smith caution that any specific listing of individual features of the FAS which are thought to be essential to the FAS diagnosis could be arbitrary and misleading. Thus, they have been reluctant to positively identify an individual as affected by ethanol without some alteration in brain function, growth, and facial appearance. They stress that

until more knowledge has been accumulated, less than complete expression of FAS can only be referred to as "suspected" fetal alcohol effects (4).

In Section A-3, the reproductive toxicity of ethanol in laboratory animals has been reviewed. Since it is important to consider the potential teratogenicity of alcohol in the human in the light of experimental evidence accumulated in laboratory animals, a systematic discussion of these data in relation to well established teratologic principles is in order. According to Wilson (123), there are six accepted general principles of chemical teratogenesis that have evolved from animal studies.

Principle 1. Susceptibility to Teratogenesis Depends on the Genotype of the Conceptus and the Manner in Which This Genotype Interacts with Environmental Factors.

It is well known in experimental teratology that embryotoxic effects are species and strain specific. For example, mouse embryos are usually susceptible to cleft palate induction by glucocorticoids, whereas most other mammalian embryos are not. This finding has been interpreted to mean that mice possess inborn chemical or anatomical features which make them more vulnerable (less resistant) to these agents than are other animals. This susceptibility could be related to such factors as the rate at which the hormone is absorbed, eliminated, or transformed by the maternal animal; its rate of passage across the placenta; or the nature of

its interactions within the cells and tissues of the embryo. Regardless of the mechanism by which the mouse is rendered more susceptible to the teratogenicity of glucocorticoids, it is clear that this sensitivity is, at least to some extent, genetically determined.

The thalidomide episode exemplifies the differences which can exist among species with regard to susceptibility to a teratogen. Man and other higher primates are extremely sensitive to thalidomide teratogenicity, showing a characteristic series of reduction defects of limbs and face; some rabbit and a few mouse strains react in a less characteristic way to much larger doses, whereas most other mammalian forms are quite resistant.

Other intra- as well as inter-strain differences in sensitivity to teratogenic agents (not to mention inter-species differences) are so well known as to require no further discussion here. It only need be emphasized that most such differences probably have an hereditary basis, although the precise nature may not be known because the metabolic and structural sites of action of teratogenic agents are often not known.

These considerations must be taken into account when attempting to extrapolate results from laboratory animals to the human situation. It is clear then, that results on the embryotoxicity of ethanol in laboratory animals cannot necessarily be used to establish the risk that this substance poses to the human fetus.

Principle 2. Susceptibility to Teratogenic Agents Varies with the Developmental Stage at the Time of Exposure.

It is a basic precept of biology that immature or developing organisms are more susceptible to change than are mature or fully developed ones. The "critical moments" concept of Stockard (124), has today become more generally known as "critical periods" in organogenesis. This critical period has been shown to be the time when the embryo is most susceptible to the induction of gross anatomical defects by environmental influences. Thus, the early events in organ formation have generally been found to be more sensitive to interference from extraneous influences than later ones, but "critical periods" are known to occur even during relatively late stages in the formation of some organs and systems. As the more basic organizational patterns of organ formation are laid down, the likelihood of major structural deviation naturally diminishes, and when definitive form and relationships are achieved, maldevelopment in the sense of gross defects is no longer of concern. The gross modeling that occurs during organogenesis, however, does not equip the organ to assume its ultimate functional role. The processes of cellular and tissue differentiation continue on more refined scales through histogenesis.

Histogenesis generally begins before organogenesis is completed and continues well into the subsequent growth phase of most organs. Harmful influences during histogenesis would not result in gross malformations but could certainly

result in finer structural defects at the microscopic level.

In close sequence with the progress of histogenesis is the acquisition of function. In fact a level of functional activity begins in many organs while histogenesis is in progress, but definite function is usually not achieved until histological differentiation is completed. It is thus not always possible to determine whether an agent causing functional abnormality has acted by interfering with ongoing histogenesis or has prevented the final step in functional maturation. As far as ethanol teratogenicity is concerned, experiments in animals have shown that ethanol is teratogenic, embryolethal and exerts growth retarding effects when given to pregnant laboratory animals during organogenesis. We do not know, however, whether in the human the spectrum of adverse effects (e.g., CNS deficiences, growth retardation, facial abnormalities and other malformations) referable to alcohol ingestion are produced during one specific "sensitive period" or whether each individual abnormality has its own period of sensitivity at a specific stage of gestation.

Principle 3. Teratogenic Agents Act in Specific Ways (Mechanisms) on Developing Cells and Tissues to Initiate Abnormal Embryogenesis (Pathogenesis).

Early studies in experimental teratogenesis were often interpreted as showing that particular agents produced characteristic types of malformations. Such associations of patterns of defects with causative factors were sometimes

referred to as "agent specificity", implying that each agent had the capability to elicit specific defects. As more and more causative factors were described, however, it became apparent that the composition of the patterns of defects overlapped, i.e., that different agents often produced some of the same types of defects, or the same range of defects in different proportions, or sometimes even the same defects in similar incidences. If each causative factor did not produce a distinctive array of defects, there must be some commonality in the developmental pathways between the induction, by whatever means, and the final expression of abnormality (123). Evidence has now been assembled from the available teratological literature to support the existence of some nine ways or mechanisms by which teratogenic agents impinge on developing systems to initiate abnormal development. These proposed mechanisms of initial changes are listed in Table 10.

TABLE 10. INITIAL TYPES OF CHANGES IN DEVELOPING CELLS OR TISSUES AFTER TERATOGENIC INSULT

1. Mutation (Gene)
2. Chromosomal breaks, nondisjunction
3. Mitotic interference
4. Altered nucleic acid integrity or function
5. Lack of normal precursors, substrates, etc.
6. Altered energy sources
7. Changed membrane characteristics
8. Osmolar unbalance
9. Enzyme inhibition

At the present time, the mechanism(s) of alcohol embryotoxicity is not known, and it would be inappropriate to advance any hypothesis in this regard. However, it is important to realize that alcohol embryotoxicity may produce developmental abnormalities which are not characteristic of ethanol alone. Thus, different chemicals acting by different mechanisms may induce the same types of abnormalities. As mentioned above, all the abnormalities of the FAS, taken singly, are rather aspecific since most of them are known to occur in various unrelated pathological conditions. For example, mental retardation, an important feature of FAS, can be caused by numerous other genetic and environmental conditions including chromosomal defects, inborn errors of metabolism and obstetrical and neonatal complications (25). To date, the group of abnormalities which constitute the FAS, taken together, has been shown epidemiologically to be characteristic only of offspring of mothers who are abusers of alcohol. Therefore, any study assessing the possible teratogenicity of alcohol by measuring the incidence of individual abnormalities rather than the occurrence of the FAS must demonstrate that other possible confounding factor(s) beside alcohol are not responsible for the observed developmental toxicity.

Principle 4. The Final Manifestations of Abnormal Development are Death, Malformation, Growth Retardation, and Functional Disorder

The final manifestations of abnormal development (intrauterine and neonatal death, congenital malformations, growth retardation, and functional disorders, e.g., mental

retardation) have all been reported to occur in offspring of animals treated with ethanol during pregnancy, as well as in progeny of heavily drinking mothers. Although any one or all could probably be induced by embryotoxic agents in sufficient dosage during critical periods of development such as organogenesis, certain manifestations are most likely to follow exposure at particular stages of pregnancy. Before differentation begins, the early embryo is refractory to most chemical insults; however, if dosage is sufficiently high, death of the conceptus may be induced before maternal toxicity intervenes. After organogenesis begins, malformation of specific organs or systems is produced with relative ease, reflecting the special sensitivities and needs of rapidly differentiating and growing tissues. A generalized cells necrosis insufficient to cause embryonic death could slow the overall rate of growth proportionate to the time required to replenish the lost cells; hence some general growth retardation might also occur. Functional deficit would not ordinarily be expected following damage inflicted during organogenesis per se because histogenesis and functional maturation are not conspicuous aspects of development at this time.

Whatever the difference and interrelations among death, malformation, growth retardation and functional deficit, they can all result in developmental aberrations. There is no logical basis for giving emphasis to one manifestation over another in evaluating adverse influences on developmental processes. Traditionally, congenital malformations have

been used used as the main criteria in estimating adverse developmental effects, probably because structural defects are more conspicuous; however, this does not justify ignoring the changes in mortality, growth rate, or functional capacity. Whether various ethanol-induced developmental abnormalities in humans and in laboratory animals are the result of different levels of ethanol exposure during the period of organogenesis, or are due to a toxic effect of ethanol at different stages of gestation remains to be assessed. Animal experiments may be instrumental in clarifying this problem.

Principle 5. The Access of Adverse Environmental Influences to Developing Tissues Depends on the Nature of the Influence (Agent).

Basically, there are two routes of access by which environmental influences may reach developing tissues in utero: 1) by directly traversing the maternal organism, or 2) or being indirectly transmitted through it. Examples of agents that pass directly through maternal tissues without modification, except dosage reduction, are ionizing radiations, certain microwaves, and ultrasound. Other physical agents such as extremes of heat and cold are not directly transmitted to the conceptus because the homeostatic processes of the maternal body are, at least initially, able to counteract the effects. Mechanical impact, short of major trauma, also is to a large extent absorbed by the maternal body and the hydrostatic cushions provided by the chorion and amnion.

The indirect transmission of substances from the

environment (maternal organism) to the conceptus takes place via the placenta. Chemical agents or their degradation products usually reach the embryo or fetus in some fraction of their concentration in maternal blood when this is more than negligible. Whether or nor they reach effective concentrations in the conceptus depends upon many sets of variables. Several pharmacokinetic mechanisms in the maternal organism may promptly reduce the blood concentration of any given chemical. Thus, the plasma half-life of compounds is dependent upon the processes of excretion, metabolism, plasma protein binding and distribution in the extravascular compartments (126). Ethanol, as has been described in Section B-1, rapidly distributes into the total body water, and the blood concentration of ethanol is mainly related to its metabolism to acealdehyde by alcohol dehydrogenase rather than via renal excretion.

It was once believed that the placenta served as a barrier which protected the embryo or fetus from foreign chemical. Actually, this is not the case, since virtually all unbound chemicals in maternal plasma appear to gain access to the conceptus across the placenta. Many molecules of small size (less than 600 molecular weight) and low ionic charge cross by simple diffusion, others by facilitated diffusion, active transport, pinosytosis,or perhaps by leakage. Lipophilic chemicals are known to cross the placenta and other membranes more readily than other compounds. Ethanol is a lipid soluble, low molecular weight compound. It freely crosses the placenta

and readily reaches concentrations in the fetus approximately equal to those of maternal plasma. Although most experiments have been carried out during late gestation, there is reason to believe that ethanol freely reaches the conceptus during the early stages of pregnancy as well.

The total dose of a chemical reaching the conceptus is a product of the interaction of many variables, some relating to maternal functional capacity, others dependent on the nature of the chemical itself, and yet others undoubtedly reflecting little understood characteristics of the placenta. No equation has been yet devised to express these complex interactions, in part because of all of the variables are not known, much less readily measured. However, it is well established that in the case of ethanol, the developing conceptus is exposed to approximately the same concentration of ethanol as is the mother. However, what constitutes an effective dose for the embryo is uncertain. According to Wilson (123), the embryo probably has a threshold for most chemical agents, that is, a dose below which no effects occur and above which peristent changes may be induced. As we previously discussed (Section A-3, comments) the important question pertains to how a dose of ethanol must be delivered to the embryo in order that it be toxic. Asked another way, which is more important in producing embryotoxicity -- peak concentration or duration of concentration above a given level? Translated into ethanol usage, is "binge" drinking more important in the teratogenicity of this chemical

than constant persistent alcohol abuse as in chronic alcoholic women?

Principle 6. Manifestations of Deviant Development Increase in Degree as Dosage Increases from the No-Effect to the Totally Lethal Level.

This principle concerns dosage effects generally, but is of critical importance to the current arguments about the existance of thresholds for various toxicologic effects. In the safety evaluation of new drugs and chemicals a major policy decision hinges on whether a range of dosage exists below which no adverse effect occurs. If it does, it permits compounds which may be deleterious at high dosage to be used with relative impunity at subthreshold dosage. If it does not, there is no entirely safe level, for as dosage decreases the probability of adverse effect also decreases, but theoretically does not reach zero until dosage is nil.

In typical teratological studies using laboratory animals, in which intrauterine death and malformation are the criteria for adverse effects, a no-effect level has usually been found when a suitable range of dosage has been used. The same seems to hold true as regards growth retardation, although here the matter has been less extensively explored. The only embryotoxic manifestation about which uncertainty exists is postnatal functional abnormalities; this uncertainty arises from lack of information rather than to evidence refuting the existence of a threshold. Thus, past experience and present indications are that all manifestations of

abnormal development begin to be expressed only when dosage exceeds a demonstrable threshold or, conversely, that a lower range of dosage exists at which no embryotoxic effects occur. Different thresholds have been shown to exist for different types of embryotoxity, even when caused by the same agent. In fact, a low threshold for one manifestation, e.g., embryolethality during early stages, would preclude the recognition of other /aspects of embryotoxicity (e.g. teratogenesis).

From the above considerations, it is clear that threshold value for ethanol toxicity during pregnancy probably exists. However, this value has not been firmly established; therefore, it is not known whether low doses of ethanol ingested by the mother are of toxicologic importance for the developing conceptus. Further investigations should clarify this important problem, but the results that will be obtained are likely to be complex and difficult to interpret. In fact, it is likely that a series of threshold values, rather than only one value, will be found depending upon the animal species used, the frequency of ethanol administration, the stage of gestation of exposure, and the end points measured (i.e., congenital malformations, embryolethality, growth retarding effects or postnatal functional abnormalities).

SECTION B-3: EPIDEMIOLOGICAL PRINCIPLES

Ideally, epidemiological studies relating consumption of alcoholic beverages tc pregnancy outcome should clarify the following:

1. The spectrum of embryotoxic effects produced by alcohol consumption.
2. Degree, frequency, duration, and time of alcohol consumption in relation to onset of pregnancy.
3. The etiologic importance of associated factors (i.e., smoking, drugs, malnutrition, etc.).
4. A measure of the risk involved.

In order to evaluate the problems involved and to define the areas in which our knowledge is incomplete, a brief discussion of each of the above items is in order.

1. THE SPECTRUM OF EMBRYOTOXIC EFFECTS PRODUCED BY ALCOHOL CONSUMPTION

The number of cases of FAS reported in the literature in the last few years are well over 200, and almost every affected child was born to a mother who was a medically recognized chronic alcoholic. This evidence leaves little doubt about an epidemiologic relationship between heavy and prolonged alcoholic beverage consumption by the mother and the birth of an offspring with the characteristic features of the FAS.

This syndrome appears to have epidemiological specificity since as far as I know, the FAS has not been identified in

the offspring of non-drinking mothers and it can readily be distinguished from other patterns of multiple malformations which share some common features, such as the syndrome of Cornelia de Lange, /and Smith-Lemli-Opitz, Trisomy 18, Familial Blepharophimosis, and Fetal Hydantoin Syndromes (18). Analysis of the dysmorphic features reveals that although no individual defect is pathognomonic, ocular and facial anomalies predominate (4). The presence of short palpebral fissures is a consistent and rather specific finding in the FAS (4). However, as correctly pointed out by Mulvihill et al. (18), there are three caveats in this respect: 1) palpebral fissure length is difficult to measure; 2) the normal standard was derived from an old survey of 243 white children (26,27), and 3) when standard deviations were calculated from the original data, in eight cases of FAS reviewed by these authors the palpebral fissure measurements were within two deviations of the mean, although all were below average.

Nonetheless, objective measurements are needed and criteria for measurement as well as norms and variability of palpebral fissure length should be obtained. Knowledge should be gathered as to the factors which may alter the palpebral fissure length, including gestational age, maternal race, and severe intrauterine growth retardation not associated with a chronic alcoholic mother.

As for other possible embryotoxic effects of maternal alcoholism (e.g., abortions, stillbirths, prematurity),

the data are difficult to evaluate. Many differences exist between drinking and non-drinking mothers which have not been accounted for in a number of presently available epidemiological studies (45, 85). Furthermore, experience with other environmental causes of altered embryogenesis would lead one to anticipate variable severity of FAS in infants born to alcoholic mothers. In fact, Hanson et al. (21), have attempted to correlate the occurrence of children with partially expressed FAS and "moderate" amounts of alcohol consumption by the mothers. Although their paper is intriguing, the results obtained so far must be interpreted with caution.

Thus, the FAS is characterized by a pattern of developmental abnormalities including mental retardation, microcephaly, intra- and extrauterine growth retardation and other associated major and minor abnormalities (4). Some of these abnormalities are aspecific in that they are known to have multiple etiologies (127). As Clarren and Smith (4) cautioned (see Section B-2), a specific listing of individual features of the FAS which are thought to be essential to the FAS diagnosis could be arbitrary and misleading. At present, an epidemiological relationship has been established only between chronic alcoholic mothers and the occurrence of offspring who possess alterations in brain function, growth and facial appearance (i.e., the full blown FAS syndrome). Until more knowledge is accumulated, the identification of cases in which the FAS is less

completely expressed, as was attempted by Hanson et al. with moderate doses of alcohol, can only be considered tentative (4).

At the present time, there is no clear epidemiologic evidence of a relationship between partially expressed FAS and alcoholic beverage consumption by the mother. Future research should clarify this important hypothesis.

2. AMOUNT, FREQUENCY, AND TIME OF ALCOHOL CONSUMPTION IN RELATION TO PREGNANCY

Detecting and quantifying alcoholic beverage consumption in any population is not an easy task, particularly when another dimension (i.e., pregnancy) is introduced as a variable. In order to better understand the progress made and the problems still remaining, the methodology for determining alcohol consumption during pregnancy used by two ongoing American studies of alcohol and pregnancy outcome is described.

The Boston University School of Medicine Program (34,38). In May, 1974, a prospective study was begun at the Boston City Hospital. After informed consent had been obtained, women registering for prenatal care were interviewed with a structured interview questionnaire. Nutritional status was evaluated on the basis of replies to the question, "What did you eat yesterday and were yesterday's meals typical?" Responses were analyzed according to the recommended dietary allowances of the National Research Council. Adequacy of nine nutrients was assessed on the

basis of the recommended diet for women 20 to 30 years old.

Specific inquiries were made about the present and past use of alcohol, tobacco, narcotics, sedatives, amphetamines, hallucinogens and marihuana. No data were available on fathers, nor could blood samples on mothers be obtained for vitamin levels and other chemical determinations. Beginning in July, 1975, women were interviewed again after delivery to record changes in drinking and nutritional patterns during the pregnancy.

The volume and frequency of maternal alcohol intake was determined, with separate inquiries made as to the use of wine, beer and distilled spirits. Drinking patterns were classified using the Volume-Variability Index of Cahalan, Cisin and Crossley (128). The total monthly volume of alcohol was calculated by multiplying frequency of use of each beverage by the various quantities usually consumed. Division by 30 yielded the daily volume. Variability of alcohol intake was established as either high maximum (five or more drinks on an occasion) or low maximum (never consuming five drinks). Women who drank less than once a month were classified as abstinent or rare drinkers and placed in Group 1. Heavy drinkers constituted Group 3. They consumed five or more drinks on occasion and also had a consistent daily average of more than 45 ml. of absolute alcohol. All women who drank more than once a month but did not meet the criteria for heavy drinkers were classified as moderate drinkers and placed

in Group 2.

Pregnancy and Health Study Project (University of Seattle) (21, 42, 49, 119) - The subjects were 1,529 pregnant women participating in a larger study of ingestions during pregnancy and subsequent health and development of the offspring. All women receiving prenatal care by the fifth month of pregnancy at two large Seattle hospitals were eligible for the study if they lived within 20 miles of Seattle and did not anticipate moving away. Only subjects agreeing to participate in the entire longitudinal study were interviewed. An acceptance rate of 85% was obtained from those considered eligible for study.

Interviews were conducted over a one-year period in 1974 and 1975. Whenever possible the interview was conducted in private, in the absence of children or husbands. Subjects were assured that information from the interview was for research purposes only and would not be incorporated into their medical record unless they so desired. Women were given the 35-minute interview in their own homes or at a place of their choice by one of the seven trained interviewers using standardized procedures. Both questions and answers were given verbally, with all recording done by the interviewer. The entire interview included questions on pregnancy history and personal statistics, smoking habits, beverage consumption habits during and prior to pregnancy, changes in habits during pregnancy, reasons for drinking and problems due to drinking, drug and medication ingestion during pregnancy, and diet.

The beverage consumption interview was similar to that used by Jessor et al. (129) and Cahalan et al. (128). For each of the beverages (wine, beer, and liquor) women were asked how frequently they drank (with forced-choice answers ranging from "never" to "three or more times a day") and how often they drank each of the quantities "five or more," "three or more," or "one or two" glasses. Forced choice answers ranged from "never" to "nearly ever time." These quantity-frequency-variability questions for alcohol were preceded by identical questions regarding consumption of coffee and tea and followed by identical questions regarding soft-drink consumption.

Each interview involved two time periods: the five months since the onset of pregnancy, referred to as "during pregnancy," and the month prior to pregnancy, referred to as "pre-pregnancy". Four alcohol scores were derived from this part of the interview; adequate test-retest reliability of these measures over a one-week interval was demonstrated (130). The four alcohol scores obtained from this part of the interview were:

1) The AA score (Jessor et al., 1968) (129), is a continuous variable representing average ounces of absolute alcohol consumed per day. It is a composite score of all types of alcohol consumed and is calculated according to the amount of absolute alcohol consumed in each drink.

2) The VV Index (Cahalan et al., 1969) (128), is a

volume variability score that categorizes total alcohol consumption into 11 non-ordered categories according to subjects' average daily volume and daily variability. Thus this score gives a measure of the massing and spacing of total drinking behavior.

3) The QFV Index, quantity-frequency-variability (Cahalan et al.,1968) (128), yields five ordered categories of drinking behavior. Rather than summating across types of beverages drunk, this score reflects the quantity and variability of consumption of the most frequently consumed beverage, combined with the frequency of drinking any alcoholic beverage.

4) Beverage-specific QFV scores were also calculated, yielding a separate QFV for wine, beer and liquor.

In addition to the above four scores which were all obtained from the quantity-frequency-variability part of the interview, four other alcohol scores were utilized, each deriving from a separate part of the interview:

5) The "Reasons for Drinking Scale" used in this study is identical to that utilized by Jessor et al.(129), and derives originally from Mulford and Miller (131, 132). This scale includes 25 statements presumably reflecting reasons why persons drink. Of these, 14 statements are recorded as a "personal-effect" score, presumably reflecting the degree to which a subject admits to drinking for personal reasons rather than social reasons. Previous research has shown some relationship between drinking for personal

reasons and alcohol problems (119).

6) The Alcohol Problems Scale, which derives from Rimmer, Pitts, Reich and Winekur (133), consists of four questions regarding serious alcohol-related problems in the areas of marriage and family, job, trouble with the law and/or hospitalization. The score reflects the number of alcohol-related problems ascribed to by a subject (range 0-4).

7) A Number of Intoxications Scale was constructed for the present study. Each subject was asked, "Have you been drunk or intoxicated during pregnancy?" Subjects responding affirmatively were asked to recall each occasion of intoxication during pregnancy and to report the amount and type of alcohol consumed, the duration of drinking on that occasion and when during pregnancy the intoxication occurred.

8) An additional alcohol scale, called "Supplemental Questions," was used for subjects reporting that they drank the maximum amount (five drinks or more at a time) on the quantity-frequency-variability interview. Using a procedure developed by Room (134) for assessing problem drinkers, subjects were asked how frequently they drank each of the following amounts: 5-7, 8-11 drinks, or 12 drinks or more. This set of questions differs in one important way from the quantity-frequency-variability questions. While the latter inquires about each kind of beverage separately, and the total alcohol consumption is

calculated later, the supplemental questions ask the subject to combine across categories of alcoholic beverages in order to determine the total number of drinks (all beverages combined) that are consumed on one occasion (119).

LIMITATIONS OF THESE EPIDEMIOLOGIC METHODOLOGIES - In their elegant paper, Streissguth et al.(119) point out that there are some limitations in estimating alcohol consumption by the various scoring systems. Thus, although at a cut-off consumption level of 1 ounce of absolute alcohol per day, the AA scale and the QFV Index each identify the same number of women as "heavy drinkers," the actual women identified by each scale are considerably different. Only a little over half of these "heavy drinkers" are simultaneously identified by both scales.

The AA scale is weak in picking up binge drinkers (subjects drinking five or more drinks at a time), particularly when the binging is infrequent. In addition, the AA misses 80% of the women who report being intoxicated at least once a month during pregnancy, as well as all the women who report serious alcohol-related problems. The AA scale is particularly good at picking up heavy wine drinkers, poorer at picking up heavy liquor drinkers and misses over half of the heavy beer drinkers. The main advantage of the AA score is its continuous nature, thus discriminating among subjects with very heavy alcohol ingestion.

The relationship of VV to QFV is also much poorer for pregnant women compared to data presented by Cahalan et al.(128) for men and women drinkers combined. The VV Index picks up a higher proportion of the heavy wine drinkers, but misses one-fourth of the heavy liquor and heavy beer drinkers. Compared to the AA, the VV picks up more of the women reporting at least one intoxication during pregnancy and more of the women reporting serious alcohol-related problems. However, half of these are still missed by the VV.

The number of intoxications does show some relationship to heavy drinking in that most subjects reporting higher numbers of intoxications are also heavy drinkers by both AA and VV. The predictive value of the intoxication scale used alone would have few false positives but a very large number of false negatives. Some very heavy drinkers report no intoxications and would thus be missed. As an example reported by Streissguth et al.(119), one woman with an AA score of 25.76 ounces/day, reported no intoxications.

The number of alcohol-related problems is also a poor predictor of current drinking practices. Some pregnant women reporting problems had stopped drinking and were abstainers; some were apparently only infrequent but severe binge drinkers. The vast majority of the heavily drinking women in the Seattle study reported no alcohol-related problems. As pointed out by Streissguth et al.(119), this may be due to the fact that the items in the scale they used included only four of the most severe alcohol-

related problems.

While the above discrepancies have involved primarily scales deriving from the same interview, two basic problems with the QFV interview are the low ceiling for maximum number of drinks per occasion and the inability of the interview to accomodate a summation of drinks per occasion across different types of alcohol.

The addition of the "Supplemental Questions" to the usual QFV interview is recommended for identifying the potentially high risk drinkers. In addition, the "number of intoxications" scale has been recommended to help identify the timing of periods of high alcohol intake. Further questions regarding specific incidents of intoxication can also be asked to clarify the duration of intoxication, and both the types and amounts of beverages consumed.

The elusiveness of the high risk drinker is best described by one woman who scarcely drank at all during pregnancy (119). She was categorized an "Infrequent" drinker on the VV Index during pregnancy, a "Moderate" drinker on the QFV, and her AA score was so low (0.06 ounces of absolute alcohol per day) as to be inconsequential. If only the AA and/or VV scales had been used she could easily have been placed in the control group as an infrequent drinker. However, the question on intoxications during pregnancy picked up two binges, one at six weeks gestation in which she drank five bottles of tequila and three beers in a four-hour period and another at 12 weeks in which she drank a six-pack of beer and two bottles of table wine in

a four-hour period. The QFV and VV indexes had no mechanism for dealing with the combined effect of the two types of liquor while the AA, which does summate across beverages, averages the quantity out over so many days that the daily rate becomes insignificant. In addition, neither scale could accurately reflect the amount in excess of five drinks that she consumed on these occasions, although this information was picked up by "Supplemental Questions." Outcome studies in which such drinking patterns are of interest will miss subjects like this if only the QFV interview is used.

The poor inter-relationship of the numerous alcohol scores suggests that the validity of this type of alcohol consumption data may not be high. Part of this problem may be due to the attempt to oversimplify relatively complex drinking activity by reducing it to a single scale or a small number of categories. It is therefore probably advisable to use multiple alcohol assessments in attempting to correlate alcohol consumption by women and pregnancy outcome.

In addition to uncertainties about the amount and frequency of alcohol consumption, the methodology of these studies does not give us an accurate measure of alcohol consumption during early embryogenesis when most drugs are known to exert teratogenic effects (123).

In the Pregnancy and Health Study Project in Seattle,

an attempt has been made in this regard, but their methodology is not above criticism. As reported above, they estimated by interview at 5 months the alcohol consumption by the mother during two time periods: the five months since the onset of pregnancy, referred to as "during pregnancy," and the month prior to pregnancy, referred to as "pre-pregnancy." However, in a later publication from the same Project, the terminology of the latter group was changed to "alcohol intake prior to recognition of pregnancy" (21). Thus, it is not clear whether the alcohol consumption was before pregnancy or during early pregnancy. This issue may be of critical importance for understanding the etiology and pathogenesis of FAS . Thus, at least in this country women generally recognize that they are pregnant at about 6 weeks from their last normal period. At this time, the human conceptus is four weeks old and undergoing active organogenesis. Therefore, alcoholic consumption when pregnant women are "waiting for their period" and do not know they are pregnant may be one of the most critical factors in establishing alcohol teratogenicity.

In summary, present available epidemiologic data on embryotoxicity of ethanol during pregnancy have been obtained using techniques that do not measure alcoholic consumption precisely. Subjects identified as "heavy drinkers" by the AAA, and QFV, and VV scores are frequently not the same subjects (119). In addition, information obtained from retrospective interviews about drinking habits in early pregnancy tend to be inaccurate since the possibility of

memory bias exists (135), particularly in the occasional binge drinker.

3. THE ETIOLOGIC IMPORTANCE OF ASSOCIATED FACTORS

The effect of maternal alcoholism, particularly in relation to incidence of abortions, stillbirth and neonatal mortality, prematurity, weight-height deficiency, and mental retardation with peculiar facial features, is a complex problem. The similarity in the overall pattern of anomalies in the children of chronic alcoholic mothers suggests a single etiology, most likely environmentally determined by some as yet unknown alteration in maternal metabolism. Regarding direct toxicity to the developing fetus, the most obvious possibility is ethanol itself. Other possibilities involving direct toxicity include a metabolite of ethanol, such as acetaldehyde, or an unknown toxic agent in the alcoholic beverages consumed. The adverse effect on growth and embryogenesis of maternal chronic alcoholism could also be the indirect consequence of generalized maternal undernutrition or deficiency of a specific nutrient or vitamin (2). Thus, exposure of the developing conceptus to alcohol may not be the only toxic factor in determining the poor pregnancy outcome in alcoholic women, but other contributing factors may also be at work.

It has been epidemiologically determined that the heavily drinking mothers are older and of high parity as compared to non-drinking or light-drinking mothers (40). They have a poor weight gain during pregnancy (2), are

more likely to experience bleeding during early pregnancy, and they have a history of more children with low birth weight (33). Furthermore, heavy alcohol consumption is highly correlated with cigarette smoking (21, 33, 40, 42) and to a lesser extent with caffeine use (35) and chronic alcoholic mothers frequently present clinical signs of malnutrition (136). All these factors with alcohol intake are known per se to represent an increased risk of poor pregnancy outcome (112, 137).

According to Mau and Netter (35), isolated alcohol consumption per se is not the only reason for the unfavorable outcome of pregnancy in chronic alcoholic mothers, but is part of a multiplicity of unfavorable factors associated with this type of patient including possibly her constitutional and character type. Whether this hypothesis has any validity remains to be assessed, but it points out our present lack of knowledge about the importance of associated factors which may contribute to the occurrence of abnormal offspring in chronic alcoholic mothers.

Therefore, any study design investigating the relationship between alcohol intake by the mother and pregnancy outcome should consider the possible confounding factors. Unfortunately, the confounding factors are numerous and not always well identified. Factors such as maternal age and socioeconomic status are clearly related to pregnancy outcome, thus making the selection of the population to be observed critical. But these are not the only factors. For example, prematurity and low birth weight are related (or possibly related) to innumerable high-risk factors

including socio-economic status, inadequate prenatal nutrition, maternal childhood factors, inadequate prenatal care, pregnancy spacing, maternal age, birth order, marital status, toxic substances ingested including legal and illegal drugs, maternal infections, toxemia of pregnancy, ethnic group, and genetic make-up (138).

Although some studies have attempted to control for a number of the known confounding variables, our knowledge is at present too limited to evaluate the relative importance of each of these factors in determining the poor pregnancy outcome of chronic alcoholic women. Furthermore, if prospective epidemiologic attempts are made to evaluate pregnancy outcome in drinking, but not medically recognizable alcoholic mothers, the design complexity of such a study is greatly increased.

Sample size and type of the population to be considered, accurate and objective measurement of alcohol intake in relation to stages of pregnancy, controls for the numerous medical and obstetrical confounding factors, and establishment of the validity of the end points measured, are problems that should be carefully considered. These problems require resolution before initiation of any epidemiologic survey.

We urgently need epidemiologic studies on alcohol toxicity during pregnancy which utilize approaches to the problem in its total complexity. It is only in this way that the results obtained will be relevant to entire

populations.

4. A MEASURE OF THE RISK INVOLVED

The present available data are not sufficient to accurately establish the incidence of FAS in the general population and the relative risk for a drinking mother of producing an affected child. However, some attempts have made in this respect. Jones and Smith (139) reported that 43% of the pregnancies of 23 chronic alcoholic mothers had been an adverse outcome. Four of the offspring died in the perinatal period and 6 FAS cases were diagnosed in the survivors. The same group of workers reported in another publication (140) that the risk of poor fetal outcome for chronic alcoholic mothers is in the range of 30-50%.

Hanson et al. (21) speculate that the risk of having an affected newborn increases proportionately with the average daily alcohol intake of the mother during the month prior to recognition of her pregnancy. According to them, "if the maternal ingestion is less than one ounce of absolute alcohol per day, the apparent risk for abnormalities appears to be low. In the range of 1 to 2 ounces of absolute alcohol per day, the risk may approach 10%. Among women who drink an average of 2 or more ounces of alcohol daily, 19% had infants who were considered abnormal." Unfortunately, this attempt to establish a dose-effect relationship is as provocative as it is premature.

Except for two infants born to mothers who were chronic alcoholics, they did not find any additional cases of FAS

using the criteria described by Clarren and Smith (4). They did, however, attempt to identify features compatible with fetal alcohol syndrome (i.e., partial expression of FAS) by examining 163 infants preselected by a research assistant in pairs: one new born from a drinking mother (AA≥1.0/day) and the other from an abstainer or light drinking mother (AA<1.0/day), delivered on the same day and at the same hospital. (It is peculiar that a study utilizing paired controls had an odd number (163) for total subjects examined.) In this study, they used as an end point findings compatible only with partially expressed FAS in which the correlation with maternal alcohol consumption has as yet to be demonstrated (4). Although an attempt was made to control for some possible confounding factors such as nicotine, caffeine and drus usuage, the sample size was too small to draw any firm conclusions, particularly concerning any dose-effect relationship as between the risk of producing an abnormal offspring and maternal alcoholic beverage consumption before and/or during pregnancy.

At present, the effects on the unborn child of "moderate" doses of alcohol ingested by the pregnant woman are not well defined. The only clear relationship between alcohol consumption and abnormal offspring is that of an increased incidence of FAS in children born to chronic alcoholic mothers. The incidence of FAS is reported to be 1-2 per 1,000 live births (4), and the frequency of possible partially-expressed FAS (4) has been estimated at 3-5/1,000

live births. Similarly, Dehaene et al. (141), reported an incidence of FAS in offspring of chronic alcoholic mothers of 2.6-3.9 per 1,000 deliveries in the years 1975-1976 in two hospitals in Roubaix, France (Table 11).

Table 11.

Incidence of the FAS* in Two Hospitals in Roubais, France (141).

Hospital	Year	No. of Deliveries	FAS	FAS Incidence (Cases per 1,000 Deliveries
Maternite Pierre de-Roubaix	1975	2,438	9	3.69
	1976	2,570	10	3.89
Ville de Roubaix	1975	3,487	9	2.58
	1976	3,440	11	3.20

*as described by Lemoine et al (1)

On the other hand, Kaminsky et al. (33), examined the pregnancy outcome of 509 Parisian mothers who drank more than 40 cl of wine (ethanol content 11% v/v) at the beginning of pregnancy. This group of mothers experienced more stillbirths and had lower birth weight infants, but there was not an increased incidence of prematurity or congenital malformations. There is no information as to the total number of chronic alcoholic women in the 107 mothers who consumed more than 60 cl of wine equivalents per day, and the lack of teratogenic effects in children of heavily drinking mothers was surprising (41). However it is likely that this can be attributed to a lower maternal alcohol intake than in the study by Ouellette et al. (34).

Since different patterns of drinking exist in different countries, regions of a country or among different ethnic groups, and since these differences are at least in part responsible for a different percentage of chronic alcoholics in different drinking populations (116), one tends to hypothesize that factors in addition to daily alcohol consumption may determine the risk of having a child with the FAS.

At present, these hypothetical factors are ill-defined, but it is conceivable that they can be delineated by prospective epidemiological studies of the sociological and medical characteristics of heavily drinking mothers who will deliver abnormal as well as normal children. Thus, an understanding of why an alcoholic woman delivers a normal child may be of importance in attempting to define the teratogenic properties of alcohol in the human.

SECTION C: SUMMARY AND CONCLUDING REMARKS

The effect of alcholic beverage consumption on outcome of pregnancy is a complex problem that tends to branch out from the scientific and medical environment because of its social and economical implications. Historically, when attention is focused on such types of problems with possible multifactorial socio-economic consequences, the interpretation of the available data tend to become somewhat distorted. It is difficult to make policy decisions without an objective viewpoint of the available evidence. My duty, therefore, as I interpreted it, was to review and evaluate the available scientific medical data on alcoholic beverage consumption and outcome of pregnancy, and report my findings to the Department of the Treasury.

I have tried in particular to examine the scientific validity of the conclusions drawn by the various investigators according to presently known and accepted principles. If additional evidence will be forthcoming, or if I have unintentionally failed to consider some evidence, I am ready to modify my judgment. However, the conclusions that I have reached so far as to alcohol consumption and outcome of pregnancy can be summarized as follows:

1. A series of rather aspecific abnormalities have been grouped into a "syndrome" which shows a remarkable reproducibility in that it has been observed only in offspring of chronic alcoholic mothers. Because of its etiologic relationship with heavy maternal alcohol consumption, it has been termed the Fetal Alcohol Syndrome (FAS).

2. The FAS is composed of constellation of abnormalities grouped into four categories:
   a) central nervous system dysfunction;
   b) growth deficiencies;
   c) cluster of facial abnormalities; and
   d) variable major and minor malformations
3. Some alteration in brain function, growth and facial appearance are essential for the diagnosis of the full-blown FAS. It is important to realize that a relationship between maternal alcohol consumption and the production of affected offspring has been demonstrated for the full-blown FAS only. At present, the relationship between maternal alcohol consumption and "partially expressed" FAS is hypothetical.
4. There are more than 200 cases of FAS infants described in the literature, and these reports establish the teratogenicity of alcoholic beverage consumption in the human, provided that:
   a) the mother has been suffering from long-standing chronic alcoholism, and
   b) the alcohol intake in relation to the affected pregnancy was heavy (on the order of at least 5.0 ounces of absolute alcohol per day).

5. Some epidemiologic studies did not find the FAS in offspring of heavily drinking mothers. It is not known whether this was due to the inability of the investigators to detect the affected infants, or to the actual absence of FAS infants in the population studied.
6. There are data in the literature indicating that besides the FAS, other alcohol-induced toxic effects on pregnancy outcome are possible. Decreased birthweight and increased stillbirth rate have been described as outcomes of pregnancies in mothers who persistently drank more than 1.48 ounces of absolute alcohol per day during pregnancy. Anomalies "suspicious of" or "compatible with" alcohol effects have been reported in offspring of mothers who drank at least 1.0 oz. of absolute alcohol per day during the month prior to recognition of pregnancy. Although the data are difficult to interpret, they certainly do not demonstrate a cause-effect relationship between the described abnormalities and "moderate" maternal alcoholic beverage consumption.
7. Although heavy alcohol consumption by the chronic alcoholic mother appears essential for the occurrence of infants with the FAS, the mechanism by which these adverse effects are produced is not known. It is particularly unclear at this time what role factors such as malnutrition, medical complications (e.g., delirium tremens, cirrhosis) and poor personal habits (cigarette smoking, drug abuse) may be playing in this process; these factors are associated with

chronic alcoholism and are known to be related, per se, to poor pregnancy outcome.

8. Experiments with laboratory animals showed that alcohol possesses a variety of toxic effects on reproductive processes. Ethanol given to animals during pregnancy is embryolethal, teratogenic and induces intrauterine growth retardation. The results, however, vary depending upon the animal species, the dose, the dosage regimen, and the time of pregnancy at which treatment is given. Although the results obtained in laboratory animals are supportive of a toxic effect of ethanol during pregnancy, it must be remembered that animal data cannot with confidence be extrapolated to the human, since at present there is no animal test or battery of tests that can predict human teratogenic risk with complete assurance.
9. Additional summarizing statements are included in the answers to the FASP Questionnaire given below.

QUESTIONNAIRE: FASP

1. Is there a minimum "safe" level of alcohol consumption which poses no risk to the fetus from FAS, or does any consumption of alcohol produce risk?

At present, it is not known whether there is a minimum "safe" level of alcohol consumption or whether any consumption of alcohol produces some risk to the fetus.

So far, a clear relationship between alcoholic beverage consumption and poor pregnancy outcome has been demonstrated only for heavy and prolonged maternal alcohol abuse. Thus, offspring with the FAS are typically born of mothers with a long-standing history of chronic alcoholism.

In the few cases of FAS reported in which alcohol intake has been documented, maternal alcohol consumption has been 150 g or more daily (91). Moreover, since most of the mothers of children with FAS were known chronic alcoholics months or years before the affected pregnancy, the importance of the time-span over which heavy alcohol intake occurs to ethanol teratogenesis is not known.

Although some attempts have been made to correlate poor pregnancy outcome with levels of alcohol consumption not necessarily related to maternal chronic alcoholism, available results seem conflicting as far as alcohol teratogenicity is concerned. Rosett and his colleagues (34, 38, 142) found that progeny of heavily

drinking mothers (mean daily intake of 120 gm of absolute alcohol with one third drinking from 236 to 473 gm) have a significantly higher incidence of anomalies than progeny of "moderate" or "rare" drinking mothers. Hanson et al. (21) reported some abnormalities of growth and development "suspicious of alcohol toxicity" in offspring of mothers who drank one ounce or more of absolute alcohol per day during the month prior to the recognition of pregnancy. On the other hand, Kaminsky et al. (33) in the best controlled prospective study performed so far, found no significant increase in congenital abnormalities in offspring of 509 women who had been drinking more than 40 cl of wine equivalents or less per day (1.48 oz. AA/day). The only toxic effects they were able to demonstrate when the heavy drinking maternal population (>40 cl wine equivalents/day) was compared to the low intake (≤40 cl wine equivalents/day) group of mothers were significantly increased incidences of stillbirths and of offspring with low birth weights and low placenta weights.

However, the authors specifically pointed out that this figure should not be construed as a "threshold" but rather as a point of departure into an area of alcohol consumption where the mounting risk is understood. Since they assume that the highest reported alcohol consumption rate is an underestimate, a genuine "threshold" level would have to be raised substantially (33).

As has been previously pointed out (Section B-2), a series of threshold values rather than a single one are likely to exist for ethanol toxicity during pregnancy. In experimental teratology

we have learned over the years that there are different threshold values depending on whether the endpoint of toxicity measured in the offspring is embryolethality, intrauterine growth retardation, or congenital malformations. Furthermore, the threshold value for each of these toxic effects depends upon the amount, frequency, duration, and gestational stage at which the developing conceptus is exposed to the chemical considered. Threshold values for ethanol exposure in laboratory animals are not firmly established, but even if they were, they could not be extrapolated to the human, since species differences in sensitivity to chemical teratogens is a well-known phenomenon (see Section B-2, principle 1 of chemical teratogenesis).

In summary, evidence so far indicates that to produce the FAS as described by Clarren and Smith, the level of alcohol consumption must be sufficiently high to cause an easily recognizable chronic alcoholism in the mother. However, evidence indicates that with lower levels of alcohol consumption, the FAS is highly unlikely although some other poor pregnancy outcome (e.g., low birthweight, stillbirth) appears possible. Although the likelihood exists that there is a "safe" level or pattern of ethanol consumption which is not associated with any toxicity during pregnancy, a numerical value for this amount is not available. Prospective epidemiological studies are required to establish whether, for example, wine (2-3 glasses) with dinner or one martini before dinner taken by the mother are devoid of any toxicity for the unborn child. The position taken by the

March of Dimes in advising women about alcohol consumption and pregnancy is prudent. Until more data is accumulated in this respect, they advise any woman who is planning to become pregnant to abstain from consuming alcohol-containing beverages (143).

(FASP Questionnaire Con't.)

2. Several studies have indicated that consumption of 3 ounces of 100 percent alcohol produces a risk to fetal outcome. What is the frequency of consumption of such an amount to produce FAS?

As far as I know, there are no published cases at this time in which the maternal ethanol intake of 3 oz. of absolute ethanol once, sporadically, or daily before and/or during pregnancy has been associated with offspring suffering from the FAS as described by Clarren and Smith (4). Although the existence of chronic alcoholism in the mother has been well documented as a prerequisite for the FAS, few estimates of actual alcohol intake have been given (91).

The mother of one patient with FAS described by Jones and Smith (139) was recorded as drinking two quarts of red wine daily (about 175 g of ethanol = 7.5 oz.). Seven cases of fetal alcohol syndrome were reported by Mulvihill et al. (18); one mother "daily consumed 6 cans of beer and a quarter of a liter of scotch", a total of about 150 gm (6.4 oz.) of absolute alcohol. Majewski et al. (144) reported 68 cases of FAS in which the maternal average daily consumption was 202 gm (8.6 oz.) of absolute alcohol. One of the lowest reported figures for maternal alcohol consumption associated with the birth of an FAS infant is 5.4 oz. of absolute alcohol per day during the month prior to recognition of pregnancy, and in this instance the mother showed clear signs of chronic alcoholism (21).

However, as pointed out in the answer to Question 1, poor pregnancy outcome has been found in women whose alcohol consumption has been less but the role played by ethanol in determining such an adverse effect is not clear. (See Section B-3 for additional discussion). If these tentative epidemiological results and some of the teratologic studies performed in laboratory animals are taken as an indication of alcohol toxicity during human pregnancy (85), then alcohol consumption less than 5.0 oz. of AA per day can be considered to be associated with some adverse effects on human pregnancy. This is probably the reason for the statement of Dr. Noble, Director of NIAAA, quoted in the Morbidity and Mortality Weekly Report from the Center for Disease Control, Atlanta, Ga. (June 3, 1977, vol. 22, #22). The comment was made that "there is a substantial and serious risk for the fetus when the woman chronically drinks 3 or more oz. of absolute alcohol (6 drinks) a day."

It is important to realize that the selection of 3 oz. of absolute alcohol per day as a point at which the risk to the fetus begins to be substantial has been an intelligent guess, mainly by extrapolating animal teratological data into the human situation (145). However, this has not been documented in the human, and it would therefore be scientifically incorrect to maintain that the chronic intake of 3 oz. of absolute alcohol per day by the mother has been proven toxic to the human fetus.

(FASP Questionnaire Con't.)

3. What, if any, are the critical periods during gestation, when alcohol consumption would be most detrimental to the fetus?

Since the FAS has been observed in offspring of women who have been chronic alcoholics for a long time before pregnancy and who usually continued to drink during pregnancy, it is not possible to establish whether there is a crucial period(s) during gestation when alcohol consumption would be most detrimental to the fetus.

As discussed more fully in Section B-2 under teratologic principle No. 3, chemicals may exert different levels of toxicity at different gestational ages depending upon the type of developmental anomaly considered; but at the same time, different doses of the same compound at a specific stage of gestation (e.g., during organogenesis) may lead to a spectrum of toxic effects such as intrauterine death, growth retardation, teratogenesis, and functional abnormalities.

Although some experiments in animals indicate that ethanol can exert toxic effects when given during organogensis (58) there is no clear evidence that the most crucial period for ethanol teratogenicity in the human is in early pregnancy during morphogenesis.

(FASP Questionnaire Con't.)

4. What is the frequency of incidence of FAS in children born to women who "binge drink?" Is a one-time incidence of "binge drinking" sufficient to produce FAS in pregnant women?

Rosett et al. (146) point out that the average daily alcohol consumption during pregnancy may not be as important in the induction of congenital abnormalities as the maximum concentrations obtained during binge drinking at critical periods.

As far as I know, this hypothesis has not been substantiated. Since the FAS as described by Clarren and Smith has been observed only in chronic alcoholic mothers who had been drinking for a long time, and since the full-blown FAS has never been a consistent finding in progeny of non-chronic alcoholic women, one is tempted to hypothesize that a single binge drinking episode may not be responsible for producing the FAS. In this respect, the occurrence of FAS is more likely related to the persistence of toxic levels of ethanol during critical periods of pregnancy rather than to a single binge episode with transiently high blood ethanol levels. However, according to well-established pharmacological and toxicological principles, binge drinking, particularly during early pregnancy, may still theoretically be responsible for embryotoxic effects resulting in abortion, stillbirth, intrauterine growth retardation, and other anomalies which may be collectively termed "embryotoxic alcohol related syndrome(s)" (EARS).

(FASP Questionnaire Con't.)

5. What is the frequency of incidence of FAS in children born to women who are classified as "moderate drinkers?" What criteria is used to determine what is a "moderate drinker?"

There is not a unified, accepted description of what constitutes a "moderate" drinker, since different institutions use different criteria for defininy the moderate drinker. For example, the National Institute of Alcoholism and Alcohol Abuse (NIAAA), defines as a moderate drinker "a person who drinks 0.22 - 1.00 oz. of absolute ethanol per day" (see Table 1, page 1). On the other hand, the Boston University studies classified as a moderate drinker any woman who drank more than once a month, but who did not meet the criteria for "heavy drinkers" (women drinking at least 5 or 6 drinks on some occasions, and a minimum average of 1 1/2 drinks per day were classified as heavy drinkers in this study).

As far as the incidence of FAS in children whose mothers are "moderate drinkers" is concerned, again it is important to realize that the full-blown FAS has been seen only in offspring of chronic alcoholic mothers who by no means can be considered moderate drinkers. However, some toxicity suspicious of, or compatible with, alcohol toxicity during pregnancy has been observed with lower (greater than 1 oz. absolute alcohol per day) consumption. Even accepting that this adverse effect is due to maternal alcohol consumption, according to the NIAAA criteria, the mother would be classified as a heavy, and not a moderate drinker.

(FASP Questionnaire Con't.)

6. What is the effect of alcohol consumption on the fetus of a woman who drank prior to becoming pregnant, but who discontinued drinking after becoming pregnant?

There is little information on this important issue. Rossett et al. (142), at the New York Academy of Sciences meeting in 1977 reported that in the Boston University study on Alcohol Consumption and Outcome of Pregnancy, they observed that 15 of 42 heavily drinking mothers had significantly reduced their alcohol intake before the third trimester, and the occurrence of abnormalities among their offspring was substantially less frequent than among those who continued to drink heavily. However, these results were obtained from a relatively small sample size, and cannot be considered conclusive. The effects of discontinuing drinking during pregnancy on pregnancy outcome should be studied in women known to be alcohol abusers.

(FASP Questionnaire Con't.)

7. Do other factors, such as smoking, caffeine, general health, or nutrition, play a part in FAS? Is alcohol the sole contributing factor?

Although there is a clear relationship between heavy and persistent maternal alcohol consumption and the occurence of FAS in offpring, there are uncertainties about the actual etiologic agent and the mechanism of this type of embryotoxicity.

As pointed out previously (Section B-3), it is likely, although not proven, that ethanol in the alcoholic beverages is the chemical responsible for producing the FAS. It is not known, however, whether ethanol itself or one of its metabolites is the sole determining factor, or whether other associated factors which are likely to be present in heavily drinking mothers (e.g., smoking, caffeine intake, and general health or nutrition) play a role in establishing the risk of FAS in offspring of chronic alcoholic mothers. For a fuller discussion of this issue, the reader is referred to Section B-3.

(FASP Questionnaire Cont'd)

8. Many of the studies used animals, particularly rats. Does this have any effect on the validity of the findings as applied to humans?

At present, it is accepted that no animal test or battery of tests provides complete assurance in predicting human teratologic risk (122, 123). The best that can be achieved with negative results from animal tests is the statement that, under stipulated conditions of exposure, the probability of untoward effects in human populations will be low.

Since the thalidomide incident, progress has been made in devising test procedures that identify some potentially embryotoxic substances, but presently used procedures still do not provide adequate predictive values. This is the case, despite the many refinements in concepts and procedures that have been proposed by numerous investigators (147, 148, 149, 150, 151, 152), and the efforts of the scientific group convened by the WHO to evaluate the methods for testing drugs for teratogenicity (153). From these years of experience, it may be concluded that most chemicals can present a prenatal hazard to laboratory animals, depending upon their manner of administration, the animal species used, and upon a number of other variables as well. This is why almost all new drugs in clinical use carry a warning on the label with regard to the possible teratogenic properties when use by pregnant women is a possibility. There has been a hope that certain nonhuman primates would be more useful for teratological

screening of drugs than rodents, but an evaluation of the results thus far obtained indicates that even the monkey cannot be relied upon to mimic exactly the human or to predict the overall embryotoxic response of the human conceptus (122).

In summary, the ethanol-induced toxic effects described in the developing chicken embryo (50), and the offspring of alcohol-treated rats (53, 55), mice (56, 57, 58), and beagle dogs (59),although suggestive and supportive of the present clinical findings, do not prove per se that ethanol is embryotoxic and teratogenic in the human.

(FASP Questionnaire Con't.)

9. Is the methodology of the studies performed valid? Does a retrospective study provide as accurate information as a prospective study, or vice versa?

The methodology utilized in the available retrospective and prospective epidemiological studies on alcohol beverage consumption and outcome of pregnancy have been critically analyzed in Section B-3, to which the reader is referred.

As far as the accuracy of the information accumulated by retrospective or prospective studies is concerned, each of these methods has its own advantages and disadvantages. Retrospective studies are relatively inexpensive to carry out, at least in comparison with prospective studies. The number of subjects can be small, since the study is initiated by the identification of cases, which are often compared with a like number of controls. Even when 2 or 3 controls are selected for each case, the number of persons studied is small in comparison with the numbers needed for prospective studies. In addition, the results of retrospective studies can be obtained relatively quickly, whereas results from prospective studies take longer, sometimes requiring months or years to collect meaningful results.

The first problem with the retrospective studies is that the needed information about past events may not be available from routine records or may be inaccurately recorded. If information

is sought by an interview or questionnaire, the informant may have inadequate information about, or recall of, events in the distant past. Further, information supplied by an informant may be biased. At the time of the study, the disease has already been diagnosed in most of the cases, and as a result, informants about cases may have a different recall as to past events than informants about controls.

A final disadvantage of the retrospective method is that it cannot with accuracy estimate the incidence rate in persons exposed versus those not exposed to a given factor. Only a relative risk can sometimes be estimated from retrospective studies.

A major advantage of prospective studies is that the cohort is classified in relation to exposure to the factors before the disease or abnormality develops. Therefore, this classification cannot be influenced by knowledge that disease exists, as may be true of retrospective studies. Prospective studies also permit calculation of incidence among those exposed and those not exposed. Therefore, the absolute difference in incidence rates between groups ("attributable risk") and also the true relative risk can be measured. Another advantage of prospective studies is that they permit observation of many outcomes. For example, although prospective studies on smokers and non-smokers were originally designed to detect association of smoking with lung cancer, they also showed that smoking is associated

with the development of additional ailments including emphysema, coronary heart disease, and cancer of the larynx, oral cavity, esophagus and urinary bladder. The main disadvantage of the prospective study is that it is usually a long, expensive and large scale undertaking. A large cohort must be followed, particularly if the abnormality has a low incidence. In addition the need to follow a cohort over a long period of time (longitudinal study) results in special obstacles. Perhaps the outstanding problem is attrition, the loss of patients to follow-up owing to lack of interest, migration, or death from other causes. Other difficulties arise from changes in the status of the subject with respect to variables of interest (e.g., the subject may change area of residence, occupation, or smoking habits, leading to errors in classification of exposure). Another commonly encountered problem with prospective studies is the changes in diagnostic criteria and methods over time, affecting the classification of individuals as affected or not affected. Administrative problems include loss of staff, loss of funding, and the high cost of extensive recordkeeping required. For all of these reasons, prospective studies, even more than retrospective, should not be undertaken without careful planning.

In summary, both retrospective and prospective epidemiological studies should be carried out in an attempt to better define the relationship between alcoholic beverage consumption and outcome of pregnancy. However, since there are several pitfalls in such

studies, the methodology used and the overall plan should be carefully evaluated by using a multidisciplinary approach before beginning each study. Only under these circumstances would the results obtained be applicable to entire populations.

(FASP Questionnaire Con't.)

10. Should warnings about FAS be addressed to pregnant women, or to all women of childbearing age?

At the present time, it is not certain whether toxicity to the unborn child is a result of maternal abuse of alcoholic beverages before and/or during pregnancy. In fact, the FAS has been identified in offspring of mothers who were known to be chronic alcoholics long before they became pregnant. In addition, there are some suggestions that alcohol consumption may exert toxic effects on the human embryo in early gestation even before the pregnancy is recognized by the mother. For this reason, it would be prudent to inform <u>all</u> women of child-bearing age, rather than pregnant women only.

Furthermore, it would be of importance to alert not only women of child-bearing age, but also the corresponding male population as to possible toxic effects on progeny of chronic alcohol abuse by women.

(FASP Questionnaire Con't)

11. What types of information might be most effective in informing women of the possible risks to unborn children due to consumption of alcohol; for example, media announcements, posters, pamphlets in offices, et cetera?

I feel that I should not attempt an answer to this question, since I have little, if any, knowledge about the effectiveness different types of information dispersion systems would have in apprising women of the possible risks to the unborn child of alcohol consumption. I think that a sociologist or an expert in the public information field should study and answer this question. The abuse of alcoholic beverages is a problem of social, medical and economic importance which requires careful attention. The discovery of the adverse effects of heavy alcohol consumption by the mother on the human conceptus is by no means recent, but in view of the attention that it has gained in this country, perhaps now is a good time to re-evaluate and focus attention of the American population on the various aspects of alcohol abuse.

(FASP Questionnaire Con't.)

12. Why would a warning label on containers of alcoholic beverages be effective or ineffective in determining alcohol consumption by pregnant women who are (a) "moderate drinkers," or (b) "binge drinkers?"

I have no experience and/or knowledge of how to evaluate the effectiveness of a warning label, and therefore will not attempt to answer this question.

(FASP Questionnaire Cont'd)

13. Should a woman's physician be solely responsible for informing her of risks connected with alcohol consumption during pregnancy?

In my opinion, a woman's physician should not be solely responsible for informing her of risks connected with alcoholic consumption during pregnancy.

Present evidence indicates that a long standing chronic alcoholic condition in the mother before pregnancy may be an important factor in the development of FAS in offspring (2,144). Other data point out that drinking by the mother during the month prior to recognition of pregnancy correlates better with poor pregnancy outcome than maternal alcohol consumption during the first 5 months of pregnancy (21).

These observations would suggest that the risks associated with alcohol consumption during pregnancy should be made known to females early in life, long before they are planning to become pregnant. Ideally, women should know the risks of alcohol consumption when they are entering childbearing years. However, the teenage population is less likely to be coming in contact with members of the medical profession, since they are young by definition and in all probability healthy. Thus, physicians are much more likely to be in contact with women who are older and/or already pregnant.

From the above considerations, it appears clear that effective prevention of FAS may not be possible if physicians are solely responsible for informing women about the risks for the unborn child connected with alcoholic beverage consumption.

One possibility in this regard would be that the risks of ethanol ingestion during pregnancy be explained during "sex education" classes during junior high school and high school.

(FASP Questionnaire Con't.)

14. Misuse of alcoholic beverages results in many social problems. Should the fetal alcohol syndrome in children be considered yet another symptom of alcohol misuse, or should it be specifically singled out for warning labels, educational programs, et cetera?

Alcohol abuse has been considered the number one drug problem in the U.S.A. and in numerous other countries as well. As I see it, the problem of alcohol toxicity during pregnancy is one of many examples of the staggering damage imposed by alcohol abuse on the individual, family and society (154). From a scientific and medical point of view, I cannot find any reason why the problem of alcohol toxicity during pregnancy should specifically be singled out.

(FASP Questionnaire Con't.)

15. Would requiring warning labels on alcoholic beverage containers be justified in light of present studies, or is further research needed?

Thus far, a clear relationship between alcohol intake and poor pregnancy outcome has been established for pregnant women with long-standing chronic alcoholism. This relationship is less than clear for lower doses of alcohol not associated with maternal chronic alcoholism. There are no data as to whether one time "binge" drinking is associated with teratogenic effects in the human, or whether a decreased alcohol consumption during pregnancy has a beneficial effect on pregnancy outcome of a woman who drank previously. There is no doubt that our knowledge in this area is scanty, and that further research is needed. I do not feel that I can express an objective opinion as to whether a label on alcoholic beverage containers is justified, not only because of the lack of complete information which still exists, but also because I do not have any expertise in judging the possible effectiveness of such a measure.

(FASP Questionnaire Con't.)

16. What type of specific warning label, if any, should be placed on containers of alcoholic beverages? Provide language.

Again, since I am not an expert in evaluating the effectiveness of a warning label, I cannot provide the language which may be most appropriate.

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ADDENDUM

C. THE HALL REPORT (letter).

Seattle, Washington

September 22, 1978

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September 22, 1978

Ms. Catherine Milton
Regulations and Procedures Division
Bureau of Alcohol, Tobacco and
Firearms
Washington, D.C. 20226

Dear Ms. Milton:

I have independently and without the consultation of other individuals, reviewed all of the material which you sent me, including the 12 volumes, the senate subcommittee hearings and the additional separate papers.

I was surprised at the amount of information which has been accumulated and by the large number of studies which have been and are being done. The area of human teratogens is an extremely difficult one and for this reason I was pleased to see the sophisticated approaches, complex models, and variety of statistical methods which have been applied to the studies of the fetal alcohol syndrome. Clinical research is extremely difficult since humans do not act like laboratory animals. It is not surprising that many of the controls and research designs are not quite as "clean" as would be desired. Realistically, it may never be possible to get absolutely reliable information or perfect controls in human teratogenic studies. The fact that in such a short time (since the awareness that the fetal alcohol syndrome was an entity in 1973), this amount of data and information has been accumulated is impressive.

As a clinical geneticist, I keep informed about dysmorphology and teratology. I feel responsible to know about conditions like the fetal alcohol syndrome. In spite of that and in spite of being in Seattle, where there is obvious interest in the syndrome, I had not been aware of the extensive research and information which is currently available. I think that this is an important observation in itself, since if I was not aware of the expanding research and information, certainly the general medical community could not be expected to be knowledgeable about the fetal alcohol syndrome or the potential risks to the unborn child related to maternal alcohol consumption. Papers given at the clinical meetings I have attended over the last few years and journal articles which I have read on the fetal alcohol syndrome had not previously lead me to the conclusions which I think can be reached after review of this material. Let me first mention some aspects of the fetal alcohol syndrome which reading all this material crystallized for me, then comment on the concept of a warning label and finally specifically answer the items of the questionnaire.

Ms. Catherine Milton
September 22, 1978

204

After reviewing the material which you sent, there can be no question that the fetal alcohol syndrome exists. It does! However, what is recognized as the fullblown fetal alcohol syndrome descr bed by Jones et al. (1973, 1974, 1976), resulting from heavy maternal alcohol consumption is probably only the "tip of the iceberg". As with many human teratogens such as Dilantin (Stevenson 1977, pp. 111-112), it is probable that maternal use of alcohol during pregnancy produces two types of effects in the fetus: The first is the specific syndrome with characteristic congenital malformations (i.e., the typical fetal alcohol syndrome). The second type of affect is the production of a number of more subtle defects which probably are dependent on the size of the dose, the timing during pregnancy, the genetic background of the mother and fetus, and other interacting environmental factors (such as smoking, nutrition, medications, etc.). This second type of the maternal fetal alcohol spectrum has not yet been fully evaluated or delineated. There are strong hints of behavioral differences (Landesman-Dwyer et al. 1977, Martin et al. 1977, El-Guebaly, Offord 1977), neurologic abnormalities, psychosocial illness (El-Guebaly, Offord 1977), hyperactivity (Shaywitz et al. 1976, Morrison, Stewart 1971 and 1973, Ross 1977, Cantwell 1972, Streissguth, Barr 1977, El-Guebaly, Offord 1977), in the offspring of moderate and binge drinking mothers; however, long-term follow-up of the infants born to mothers using moderate and minimal amounts of alcohol or those born to binge drinkers has not yet been possible. The evidence that is available, together with a knowledge of what has been seen in other human teratogens, suggests to me that when further information does become available, we will see this second category of defects manifested in the children of those women who drank alcohol during pregnancy, perhaps even very small amounts or only during critical periods.

As a geneticist and from my knowledge of the work done on other human teratogens, I suspect that there are different genetic predispositions to the deleterious effect of maternal alcohol consumption on the unborn child, both with regard to the way in which mother metabolizes alcohol and that way in which the fetus metabolizes alcohol or responds to maternal metabolites. In other words, it is well known that normal genetic variations occur in human beings in many enzyme systems as to the clearance rates, metabolic byproducts produced and dose response and when these systems are stressed, disease will be more likely to occur in some genetic forms than in others. There have been documented differences in alcohol metabolism in humans (Cruz-Coke 1973, Raskin 1975, Lieber 1977, Korsten et al. 1975, Bennion, Kai Li 1976). Hanson et al. (1977) and the Boston group (Rosett et al. 1977, Ouellette et al. 1977) have already suggested that some non-white racial groups may be more susceptible to fetal alcohol syndrome. In addition, several authors (Landesman-Dwyer et al. 1977, Buckalew 1977), have suggested that males may be more susceptible to the fetal alcohol syndrome than females. I would expect there are mothers or fetuses, or a specific combination of mother and fetus who, with only very small amounts of alcohol or during critical periods in pregnancy, may develop either the fullblown syndrome, or a significant adverse effect.

Ms. Catherine Milton
September 22, 1978

The major concern to me with regard to the fetal alcohol syndrome is not the abnormal appearance or the growth retardation, but the effect on the brain in terms of permanent malformations and biochemical changes which would result in permanent changes in behavior and learning. Because of genetic differences between individuals, I would expect there to be some people who are particularly susceptible to a central nervous system effect rather than dysmorphic (abnormal appearance) features. I would anticipate that in some genetically susceptible individuals, the brain will be the organ primarily affected. In this situation, the only way such individuals would be recognized to have been damaged would be by long-term evaluations of behavioral, learning, and developmental progress. Prospective studies have not been in process long enough to have this type of follow-up, nor are they probably set up in such a way as to recognize which individuals may be particularly susceptible. One of the most distressing aspects of fetal alcohol syndrome, to me, is that the CNS effects apparently do not improve with time (Streissguth et al. 1977, Hanson et al. 1977, Clarren, Smith 1978).

The question was raised several times in the materials I read, as to whether there is a relationship between the amount of alcohol consumed and the degree of fetal involvement. Although this type of relationship has been looked for in animal studies (Randall et al. 1977) and to a lesser extent in human studies (Hanson et al. 1977, Hanson et al. 1976, Kaminski 1976), further investigation and large numbers of cases are needed to answer the question precisely. A major problem is that in human studies, the mother's own alcohol consumption history must be relied upon. Many other phases of alcohol research (Streissguth et al. 1977, Little et al. 1976), suggest that alcoholics are notoriously under-reporters of the amount of drinking which they do. Thus, the relationship between dose and fetal effect in humans will be extremely difficult to establish in "self-reporting" studies, particularly in view of the expectation that there will be individual and genetic variations in response to dose and timing.

At the same time, it is important to point out, based on experience with other human teratogens, that teratogenic compounds which cause malformations in large doses usually have an effect in small doses. The data from both smoking (Lowe 1959, Ravenholt, Levinski 1965, Miller 1974, Herriot et al. 1962) and radiation (Stevenson 1977, pp. 367-375) exposure during pregnancy clearly show, now, that large numbers of cases have been accumulated, that there is a linear relationship between dose and adverse effect, down to very low doses. Thus, not only is there an adverse effect in large doses, but small doses have a definite adverse effect as well and there is no minimum threshold. In other words, there is no safe dose.

I do not think that it is clear from available research at what time during pregnancy the worst effects from maternal alcohol consumption occur. From a classical teratologist's point of view, one would expect the worst effects to occur very early in pregnancy during the first trimester, since that is when organs are forming and that is when most other human teratogens have their major adverse effects. In the case of some other human teratogens (rubella - Hardy 1969, thalidomide - Knapp et al. 1962), characteristic malformations may

be produced only when exposure to the teratogen occurs at very specific times during gestation (i.e., on specific days or even hours). Thus, it would be expected that during the first trimester, the unborn child would be particularly susceptible to the adverse affect of maternal alcohol consumption at certain times. Because of this, binge drinking, moderate maternal alcohol consumption and even minimal maternal alcohol consumption is of concern during the first trimester.

One of the unusual aspects of alcohol as a human teratogen is that its adverse effects are probably not restricted to the early period of organ development, but rather continue throughout gestation. Since one of the major effects of alcohol is on the developing brain and the brain continues to grow, neurons migrate and cells develop through all three trimesters, it seems likely (and there is some suggestion from the available data), that maternal alcohol consumption at any time during brain development could have an adverse effect. The data available (Little 1977, Rosett et al. 1977, Streissguth et al. 1977, Ouellette et al. 1977), also suggest there is an adverse affect on growth and development with maternal alcoholism in the second and third trimester.

I strongly suspect that there is no "safe" dose or amount of maternal alcohol consumption at any time during pregnancy, because there may be some type of adverse effects at any level of maternal consumption, because there may be "critical" susceptible periods during development of the fetus which have not yet been defined, because there may be individuals who are genetically more susceptible than average, and because adverse affects can occur throughout the entire pregnancy.

It must be emphasized that fetal alcohol syndrome is a preventable disorder. Estimates of its frequency suggest the full syndrome occurs in 1-2 in 500 newborns, but other types of adverse effects are probably much more common - I would estimate as high as 1 in 50. There is no question but what it is one of the most common known causes of mental retardation. Since it is preventable, every avenue of prevention should be explored. It is clear, to me, that an extensive public education program concerning the risk of fetal alcohol syndrome and a special effort to educate women in the childbearing age, physicians, and medical personnel is needed. But the question at hand is whether there should be warning labels on bottles containing alcohol.

I was impressed by the number of reports and letters which had been accumulated from the wine and hard liquor industries. It was difficult for me to take them seriously since they are all so obviously self-serving. On the other hand, there were some specific items raised by these letters against warning labels that deserve consideration. The first is the question of whether warning labels would produce guilt feelings in the woman who had a child: A) which had been damaged by alcohol or, B) which was mentally retarded for some other reason, not related to alcohol but the mother felt guilty because she had consumed alcohol during the pregnancy. It seems to me that this is an unavoidable problem. Any parent with an abnormal child feels that there should have

been something that could have been done to avoid the problem. Whether or not something could have been done, they feel guilty and look for solutions. However, I am sure that any parent would be much more incensed and have more guilt if he or she was denied information that would have made it possible to avoid the problem.

Second is the question of whether women should have direct access to information about the adverse effect of alcohol consumption during pregnancy on the unborn child, and whether this would somehow interfere with the doctor-patient relationship. There has been an increasing availability of health care information of all kinds. The general public expects to be able to understand their own health situation and have access to health information. Most people have become more health conscious and want to practice preventative health care. Doctors must expect that their patients will be asking more sophisticated questions. I was concerned by the number of letters from physicians who indicated that they do not believe that alcohol can possibly have any adverse effect on the unborn child. I think this attitude reflects the fact that the medical community is not fully informed about the effects of alcohol during gestation and further emphasizes that this information should be directly available to the public.

The third area which I think is a legitimate concern is whether or not warning labels would have an adverse economic effect on the sale and consumption of alcohol, both nationally and internationally. The warnings would be aimed at a very small and select group of individuals, and only during specific times in their lives. If there is a parallel to be drawn from the cigarette warnings, those warnings have apparently not had a major deleterious affect on the industry and they were aimed at <u>all</u> smokers.

Finally, is the question of cost of labels. It is very difficult for me to understand how the cost of warning labels could be as great as quoted by DISCUS. An impartial estimate should be made. Whatever the case, the cost will be passed on to the consumer if it is felt that the consumer will benefit from, or has the right to, the information added to the label.

After reading the information which I was sent to review, I became convinced that if warning labels are introduced, they should be only the first step in an ongoing process of public and medical education.

In favor of warning labels are several points. The most significant is the right of the consumer to know if a product has a risk. The consumer protection movement has stressed that any consumer should be entitled to know when there is a health hazard related to that product. In this context, it would not be necessary or even relevant to determine effectiveness of warning labels since the consumer has the right to the information.

The question of previous effectiveness of warning labels is somewhat irrelevant to a warning label for the fetal alcohol syndrome since no equivalent situation has occurred. Whether or not cigarette consumption was altered by the warnings printed on packages is not at all the same kind of situation, since the warning labels on cigarette packages were directed at the health of the individual smoking the cigarettes. By contrast, in the situation of the fetal alcohol syndrome, we are talking about labeling which might alter the mother's behavior in order to protect her unborn child.

Another question about warning labels is whether there should be a general health caution as well as information relating to the fetal alcohol syndrome specifically. My personal opinion is that anything which is hazardous to one's health should be so labeled and that individuals should inform themselves about the details of that hazard and this type of information should become part of general education. It seems appropriate the bottles containing alcohol should be labeled in such a way as to imply that excess consumption can be hazardous to the consumer's health. The general public (Buckalew 1977), already has some awareness that excessive alcohol consumption can be harmful to health. However, by contrast, that the general public is not aware of the serious concern that maternal alcohol consumption in any dose at any time during pregnancy may be harmful to the unborn child. Thus, because information about the fetal alcohol syndrome is not a part of the general knowledge of the general public, warning labels are more important as a source of information. Nevertheless, a major education thrust and awareness program in addition to warning labels will be necessary. It is very clear that an extensive education program must be undertaken at the same time or in conjunction with warning labels for health care professionals, educators and the general public. One of the principle reasons that such an education program is needed, is that early pregnancy may well be one of the most critical times for the deleterious effects of alcohol. In addition, family members and husbands need to be educated so they can be supportive of their wives' abstinence from alcohol.

With regard to the specific items of the questionnaire which you provided:

1. Is there a minimum "safe" level of alcohol consumption which poses no risk to the fetus from FAS, or does any consumption of alcohol produce risk?

Based on other human teratogenic studies and the data now available on fetal alcohol syndrome, I doubt that it will be possible to establish a minimum "safe" level of maternal consumption of alcohol in humans. The data from Hanson et al. (1977), Kaminski et al. (1976), Ouellette (1978), certainly suggests a dose-response relationship. I anticipate that there are subtle deleterious affects, which have not yet been looked for or identified, but will be present in the low maternal alcohol consumption groups. In addition, as mentioned earlier, I would anticipate that there may be genetic predispositions in any given mother or fetus which would make that individual more susceptible to low doses or at specific times during pregnancy. Our current understanding does not allow for the identification of susceptible individuals. Thus, the most prudent

advice to a pregnant woman is to avoid alcohol in any dose and at any time during pregnancy.

2. Several studies have indicated that consumption of 3 ounces of 100 percent alcohol produces a risk to fetal outcome. What is the frequency of consumption of such an amount to produce FAS?

The data are not conclusive enough at this time to give such a frequency figure. There is a suggestion from the San Diego workshop on fetal alcohol syndrome and from Hanson et al. (1977), Ouellette (1978), Dehaene et al. (1977), Kaminski et al. (1976) that fetal alcohol syndrome occurs in at least 1 or 2 in 1,000 pregnancies. In addition, there is a suggestion from the Seattle group that 10-20% of heavy drinkers have children with physical features consistent with the fetal alcohol syndrome. These figures are with reference to children who have the typical physical stigmata of the fetal alcohol syndrome including prenatal growth deficiency, microcephaly, palpebral fissure shortening, mental retardation, and mid-facial abnormalities. These physical features may not be apparent to the untrained observerand thus there has probably been under-recognition of the disorders in some large studies (Rosett et al. 1977). There are convincing data from human and animal studies (Randall 1978, Chernoff 1977, Henderson, Schenker 1977, Ellis et al. 1977), that there is an increase in miscarriages, stillbirths and newborn mortality when large amounts of alcohol are consumed by the mother. These pregnancies have not been included in the attempts to establish frequencies of the fetal alcohol syndrome.

Almost surely there is a group of affected individuals with more subtle changes (i.e., perhaps primarily affecting the central nervous system), than the "classical" fetal alcohol syndrome. As I indicated earlier, I think that the frequency figures would be much higher if researchers looked for subtle neurologic differences at various ages. It would be expected that there can be structural damage to the brain (Clarren et al. 1978, Jones, Smith 1975), changes in biochemical receptivity and feedback (Phillips 1976) and changes in behavior and learning (Streissguth et al. 1977) which need not be reflected in overall growth reduction or unusual physical (dysmorphic) features. The frequency of the more subtle effects (hyperactivity, loss of 10-20 IQ points, changes in behavior, etc.) is not yet clear. The data on these kinds of subtle changes will come only after much more long term research has been conducted. Even without such studies, one must be suspicious that there is a much higher incidence than 1 in 500 of significant alteration of behavior and learning in infants exposed to "heavy" maternal alcohol consumption in utero.

Whatever the case, fetal alcohol exposure is clearly a major cause of mental retardation which is preventable. For this reason, the exact incidence is probably not as important as public awareness and public education.

3. What, if any, are the critical periods during gestation, when alcohol consumption would be most detrimental to the fetus?

It would appear both from the human and animal studies available in fetal alcohol syndrome and from work with other teratogens that the first trimester (the first three months of pregnancy) is the most critical time for affects of maternal alcohol consumption (Clarren et al. 1978, Randall et al. 1977, Rosett et al. 1977). This is in keeping with traditional teratology, i.e., that the first

trimester is the critical period in organ rormation. However, there is unquestionable evidence that maternal alcohol consumption can have some deleterious effect during the second and third trimester as well (which makes sense since the brain is still growing and neurons are migrating during that time)(Rosett et al. 1977, Little 1975). Biochemical insults which occurred during the second and third trimester could decrease cell growth even though the organs are formed. In addition, if fetal alcohol exposure does have some permanent alteration in biochemical pathways and cellular receptivity, these changes may well occur during the second and third trimester (Phillips 1976). A teratologist would anticipate that changes occurring in the third trimester would be less likely to cause major congenital malformations, but rather to bring about changes in behavior and learning patterns and intellectual development. The data available now support this concept (Hanson et al. 1977, Rosett et al. 1977). Thus, the question of "when is the crucial period during gestation", must be related to the question of "to which abnormality". Major malformations would be expected to occur during the first trimester, alterations in behavior and development and neurologic impairment may well be consequences of second or third trimester exposure. Again, the concern here is that most mothers are not aware that alcohol may be deleterious when used very early in pregnancy, even before the woman is aware she is pregnant.

There has been observed and reported by pregnant women that there may be some type of inherent mechanism which decreases the mother's desire to drink alcohol later in pregnancy (Rosett et al. 1977, Little 1975, Little et al. 1975). If this is true, these natural mechanisms would appear to have not yet gone into effect early, during what is probably the most critical period for congenital malformations.

4. What is the frequency of incidence of FAS in children born to women who "binge drink?" Is a one-time incidence of "binge drinking" sufficient to produce FAS in pregnant women?

The answer to this question has not yet been determined since many of the available studies did not even ask about binge drinking. In addition, researchers cannot really rely on the histories given by the drinking mother since drinkers are notoriously poor reporters and their memories may well have failed them with regard to specific binge drinking episodes (Streissguth, et al. 1977). I expect that there are periods in development that are "critical" for particularly high levels of alcohol or alcohol byproducts in causing either malformations or more subtle effects on the central nervous system. Thus, the exact timing of binge drinking is important in establishing whether, and what types of deleterious effect the "binges" may have. The available data suggest that binge drinking would be expected to have a significant adverse effect. It would not be surprising if it does not produce the "full" fetal alcohol syndrome, but rather an effect on neuron development, behavior, etc. However, to establish such correlations, careful documentation of the timing of the binges with long-term follow-up will be necessary. I would anticipate

from the information available that severe damage to the brain can occur from only one or two binge episodes at exactly the wrong time in a genetically susceptible individual.

5. What is the frequency of incidence of FAS in children born to women who are classified as "moderate drinkers?" What criteria is used to determine what is a "moderate drinker?"

The criterion for defining a moderate drinker have been outlined by many workers including Little 1977, Streissguth et al. 1977, Cahslan et al. 1967 There is more work needed to determine the best way of defining various drinking patterns, being able to get accurate information from the mothers, and then correlating it with the outcome in the child. I am not convinced that researchers have gotten reliable drinking histories. Perhaps regular blood levels or 24-hour blood levels of some kind or urine determinations may be required to get a reliable evaluation of maternal alcohol consumption. The incidence of fetal alcohol syndrome and more subtle deleterious effects to children born to mothers who have been classified as "moderate drinkers" is not yet clear either. It is likely to be lower than the frequency with heavy maternal drinking (Ouellette 1977). The full fetal alcohol syndrome may not even occur with "moderate" maternal drinking. Again, my major concern is that with moderate maternal drinking there can be CNS damage either subtle or severe. Long-term follow-up of the "at risk" children is needed to establish these figures. The available data do not yet indicate whether moderate drinking is of most concern during the first trimester or whether moderate drinking in all three trimesters is required to cause damage. As with most other teratogens, one would expect a dose-related effect and thus a less severe effect in moderate drinkers than in heavy drinkers, but definitely an effect. In addition, one would anticipate that there will be genetic susceptibility in some individuals such that moderate and even light drinking could have a more significant deleterious effect.

6. What is the effect of alcohol consumption on the fetus of a woman who drank prior to becoming pregnant, but who discontinued drinking after becoming pregnant?

Unquestionaly, the timing of the maternal drinking is important. The problem is to establish when a woman considers herself pregnant? It may well be that most women consider themselves pregnant only after they have a pregnancy test. They are, in fact, pregnant from the moment of conception. It is very clear that this early period may be a very critical time in terms of producing damage to the embryo from alcohol. In other words, a woman probably needs to discontinue drinking at the time of her last menstrual period to assure that she will not have a deleterious effect on the fetus. The Seattle studies (Hanson et al. 1977), suggest that there is a correlation between damage to the baby and maternal drinking during the period prior to that when the woman became pregnant. To my mind, this data suggests that the drinking pattern prior to pregnancy is carried over into early pregnancy and therefore this observed

correlation is seen. Most women are unaware of the importance of the first few weeks of pregnancy.

If the mother <u>really</u> stopped drinking at or before the time of conception, I would expect there to be no continuing adverse effect of the alcohol on the unborn child, when no alcohol is present in the mother's system. There may be, however, some effect of other features of the life pattern of a drinking mother (i.e., nutritional, vitamin intake, liver disease, etc.) which may have a different type of adverse effect and ideally should be allowed to return to normal before beginning a pregnancy. In the "best of all worlds" the woman would have discontinued drinking and developed good health habits for several months prior to becoming and recognizing herself to be pregnant. In the "real life situation", if the mother stops drinking at the time she becomes pregnant (i.e., conception), she should not wait until her first missed period, there would be expected to be little concern about the deleterious affects of alcohol on the unborn child.

7. Do other factors, such as smoking, caffeine, general health, or nutrition, play a part in FAS? Is alcohol the sole contributing factor?

There is no question but what there are additive and even synergistic effects with environmental factors and the general health of the mother (Rosett et al. 1977, Landesman-Dwyer et al. 1977, Little 1977, Martin et al. 1977). However, malnutrition alone is clearly not the problem which produces the symptoms of the fetal alcohol syndrome. In malnutrition, malformations have not been reported and the weight of the infant is less than the length. By contrast, in children with fetal alcohol syndrome, the weight is greater than the length. In addition, children whose mothers have suffered from malnutrition usually have catch-up in growth after they are born and have been fed. Children with the fetal alcohol syndrome do not have catch-up growth (Streissguth et al. 1977). The data available show that maternal smoking which alone correlates with decreased birth weight, adds to the problems of the unborn child exposed to alcohol (Martin et al. 1977). All of the factors mentioned (nutrition, caffeine, smoking and even viruses), affect fetal health (Ouellete 1977), however, the evidence is overwhelming that alcohol alone can produce multiple congenital anomalies.

8. Many of the studies used in animals, particularly rats. Does this have any effect on the validity of the findings as applied to humans?

The animal studies available corraborate the findings in humans that alcohol is a teratogen. The problem with animal studies is that no animals have exactly the same biochemistry or developmental mechanisms as humans, therefore, none is an ideal model for the human fetal alcohol effects and no animal model can entirely substitute for human studies. On the other hand, animal studies are extremely important in several respects. The first is that they allow researchers to get at mechanisms of teratogenicity and thereby identify the timing, and some genetic factors predisposing to susceptibility. Animal models may shed light on the question of "critical periods" for malformation. Animal

studies have been the basis of other teratogenic studies because of the underlying assumption (which has a great deal of support) that basic biological processes are the same in all mammals. It may be possible from animal models to determine whether binge drinking during "critical" developmental periods has an effect and whether these effects are specific or unique. Ideally, if researchers can identify the mechanism and timing of the fetal alcohol syndrome and other adverse affects on the fetus, treatment, prevention and identification of those individuals at risk could be developed.

9. Is the methodology of the studies performed valid? Does a retrospective study provide as accurate information as a prospective study, or vice versa?

I am not an expert on methodology, however, it seems clear to me that the studies which are available at this time are as good as most studies of human teratogens. Clinical studies are extremely difficult in humans since one cannot control behavior and cannot always rely on what the individual tells the researcher. Human teratogens have always been recognized in retrospect. This is not surprising and does not in any way make the observation less important. The large prospective collaborative perinatal project sponsored by National Institutes of Newborn Diseases was designed and undertaken with the aim of recognizing human teratogens like alcohol. The study did not initially identify the fetal alcohol syndrome or several other teratogenic conditions (including fetal Dilantin syndrome (Jones et al. 1974). Being a retrospective study does not invalidate observations but it is something which must be taken into account in interpreting the data. Prospective studies allow the researcher to get at subtleties and more specific questions. However, in the case of the fetal alcohol syndrome, all studies must rely on the mother to report her alcohol consumption. To my mind, both retrospective and prospective studies are necessary and important. One cannot emphasize strongly enough the difficulty involved in this type of clinical research.

10. Should warnings about FAS be addressed to pregnant women, or to all women of childbearing age?

I think that if there are warning labels they should be addressed to all women of childbearing age since probably the most critical period is early pregnancy, just after conception. In addition, it may be that the period of nursing is important in regard to deleterious effects of maternal alcohol consumption on the infant (Rawat 1977). This is an area in which further research is needed. Thus, if the warning were addressed only to pregnant women, the nursing mother might feel that she need not worry about drinking. It is necessary to make a distinction between the effect on the unborn child and the overall health effect of alcohol on the mother. The issue raised here has been the effect on the child and in that regard, the warning should be addressed to all women of childbearing age.

11. What types of information might be most effective in informing women of the possible risks to unborn children due to consumption of alcohol; for example, media announcements, posters, pamphlets in offices, et cetera?

I am not an expert in the area of public education, however, I am aware of public education efforts directed at making women aware of prenatal diagnosis and genetic counseling (Hsia 1977, Clow, Scriver 1977, Kaback, O'Brien 1973, Epstein et al. 1975, Kaback et al. 1973, Clow et al. 1973). These efforts suggest all avenues of public education are worthwhile. Public Service advertisements on TV, radio, magazines and newspapers; articles in magazines, newspapers and professional journals; distribution of literature in doctors' offices, with pregnancy testing, in public health clinics, posters, displays and bulletin boards in public places; and education programs directed specifically at high school and junior high school students, health education teachers, health related professionals and physicians, are all worthwhile. The programs outlined in Wisconsin and Texas as well as by the Wine Institute (March 15, 1978, report), all seem to be valuable guides.

I suspect that the experience gained through previous alcohol information programs may also give some insight about what will be worthwhile approaches, however, the emphasis is clearly different since the focus should be on the unborn child and prevention of problems for that child.

12. Why would a warning label on containers of alcoholic beverages be effective or ineffective in determining alcohol consumption by pregnant women who are (a) "moderate drinkers," or (b) "binge drinkers?"

It is important to give women information so that they can make their own choice. The data available from the studies of Little (1977) and Rosett et al. (1977), and Landesman-Dwyer et al. (1977), suggest that moderate and binge drinking can be controlled and modified by the woman who is pregnant. The woman's behavior in this type of drinking does not fall into the same category as the heavy chronic alcoholic woman. If there is a risk from moderate and "binge" drinking and the data overwhelmingly suggest that there is, then the mother who knew there was a risk to her unborn child would probably want to avoid alcohol consumption throughout the pregnancy so as to take no risks for her child. Little (1977), Rosett et al. (1977) and Baric, Macarthur's (1977) experiences suggest that even chronic alcoholics will try to curb their alcohol consumption in the interest of their unborn child. Not to provide such women with information that there may be a problem with moderate or binge drinking would be unfair and misleading to the mother who would have voluntarily chosen to control her drinking if she knew there was any concern. Pregnancy is a time when women are receptive to maintaining their health and thus would be expected to be a time when they would be receptive to controlling their alcohol intake. Rosett's study (1977) suggests that in a heavy drinking mother, second and third trimester reduction is probably better for fetal outcome than when no reduction has occurred. On the other hand, the data suggests that alcohol consumption should be decreased right from the very beginning of pregnancy and that not only moderate or binge drinking, but even minimal drinking may have some effect on the fetus.

Ms. Catherine Milton
September 22, 1978

13. Should a woman's physician be solely responsible for informing her of risks connected with alcohol consumption during pregnancy?

I certainly do not feel that this area is one for doctor-patient education alone. Most physicians caring for pregnant women in the past have not specifically warned against the danger of alcohol. In the past, alcohol consumption has not routinely been considered part of the pregnant woman's record. Alcohol consumption has been considered a part of dietary history, general medical history, or social history. Many physicians do not even ask about alcohol consumption. Not all doctors agree, or are informed about the potential effect of alcohol on fetuses. The doctors themselves must be educated as to the state of our knowledge about fetal alcohol syndrome and the potential danger. In addition, most women do not go to their doctors before they are pregnant and may not go until late in the pregnancy, so that clearly this information must be available to the woman prior to her care for a given pregnancy. Many women receive no medical care for their pregnancies and would have no access to such information. If information about the risk of maternal alcohol consumption during pregnancy were left to the doctor-patient relationship, the information might not be available to the mother before the suspected critical time. Most women would like to have this information in time to be of some use.

14. Misuse of alcoholic beverages results in many social problems. Should the fetal alcohol syndrome in children be considered yet another symptom of alcohol misuse, or should it be specifically singled out for warning labels, educational programs, et cetera?

Fetal alcohol syndrome is, in fact, different from other types of alcohol abuse since it affects the unborn child. I think it can be argued that alcohol abuse in a parent affects children, both unborn and born in many social ways. Nevertheless, what is happening is the fetal alcohol syndrome is different because the teratogenic effect may be a long-lasting and irreversible process. Certainly, it should be separated in the sense of pointing out that it is a different type of affect than the misuse of alcohol in the mother has on her own health and social situation. In addition, the particular concern about the fetal alcohol syndrome might be lost in an overall program on alcohol and alcohol abuse. Nevertheless, I think that it is extremely important (to make the point again), that any program of warning labels does not avoid the need for an education program that the fetal alcohol syndrome is part of the total picture of alcohol abuse. However, specific efforts should be made at this time to distinguish the fetal alcohol syndrome and deal with it as a separate phenomenon, since the general public is so unaware of the problem.

15. Would requiring warning labels on alcoholic beverage containers be justified in light of present studies, or is further research needed?

Further research is certainly needed, but warning labels are justified now in view of the information presently available and should be used for all alcoholic beverages (Kaminski et al. 1976) on all packaging material as well as the containers.

16. What type of specific warning label, if any, should be placed on containers of alcoholic beverages? Provide language.
I would favor a warning label which is a rather general warning and perhaps will need to be modified and made more specific in the future. I would recommend: "Warning: Consumption of Alcohol at any time during pregnancy may be harmful to the unborn child -- Consult your physician".

In summary then: I think the evidence is overwhelming that the fetal alcohol syndrome exists and the other more subtle deleterious affects occur in children whose mothers drink during pregnancy. The frequency of adverse effects from maternal alcohol consumption has not been determined, but I would estimate maybe as high as 1-2 per 100 births. Currently no minimum safe level of maternal alcohol consumption can be established at any time during pregnancy or at any level of consumption, thus, the most prudent advice to pregnant women is to avoid alcohol consumption during pregnancy and while nursing. The most susceptible period for detrimental effects of alcohol on the fetus is probably in early pregnancy (the first trimester), however, affects throughout pregnancy have been demonstrated. Women have the right to know that there may be a risk to their unborn child. Since the information is not general knowledge either to the lay public or the medical profession, I recommend that warning labels be required on the containers and packaging material of all alcoholic beverages. In addition, there should be a broad education program for the general public and health professionals concerning the fetal alcohol syndrome and other deleterious affects of maternal alcohol consumption during pregnancy. I hope this analysis is helpful to you.

If you have questions, please do not hesitate to contact me.

Sincerely,

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ADDENDUM

D. THE ETZIONI REPORT: "A SYSTEMATIC AND GRADUATED RESPONSE."

New York, N.Y.

September 15, 1978

TABLE OF CONTENTS

Abstract	226
General Posture	228
FAS in a Graduated Context	223
A. The Status of the FAS Data	223
B. Policy Implications: Questions of Sub-Populations	234
C. Policy Implications: Questions of Legitimacy	237
D. Conditions for Effectiveness of Labels and Other Modes of Public Warning	241
E. Potential to Cause Harm	244
F. Economic Costs	246
The Specifics of the Alert	247
Limitations of This Commentary	253

Abstract

My main recommendation is that the federal government's response to new scientific findings about the danger of alcohol consumption by pregnant women to their fetuses should not be treated as an isolated issue, but be viewed as part of a graduated and systematic approach to such public warnings. The warnings need to be graduated to d ferentiate clearly among various levels of danger (according to differences in the "strength" of the data available, the magnitude of the "disutility" caused by the product at issue, the actual or potential distribution of the "disutility" in the population, and other such factors). The main reason for these suggestions is that it seems that growing segments of the public ignore more and more of such warnings because they feel they cannot heed the recent avalanche of forbiddens ("After all, you've got to consume something"), and the most widely used tools of public policy in this area do not sufficiently help them to differentiate between more dangerous products and those which pose lesser threats.

Aside from the need to differentiate among levels of alert, and to evolve a systematic approach to them (rather than treating each in isolation), it seems advisable to curb the propensity toward an inflation of alerts, which debases their credibility. They should be used sparingly, taking into account not just the costs regulation and enforcement entail, but also their "costs" in taxing the public's toler-

ance for government intervention and in using up whatever stock of legitimacy such action still commands.

Within this context, for reasons spelled out below, the present uneven and partial status of the scientific data about FAS seems to warrant a low-level alert. For now, this may well not involve labeling of all liquor, wine, and beer containers, but only putting posters in places where such beverages are sold, and in prenatal care clinics; disseminating information to physicians, relevant educators, and women's groups; as well as providing public service announcements.

Additional studies of FAS, as well as public reaction to graduated warnings, are called for. When these are completed, a different level of alert, possibly including labeling, may be appropriate.

GENERAL POSTURE

There are growing signs of an immanent proposition-13 type backlash against the regulatory powers of the government in general, including those concerning labeling requirements, disclosure of information to consumers, etc. Among those who recently called for a "regulatory budget," for a "government-wide mechanism for assessing the cumulative impact of regulation, for setting regulation priorities, and making difficult trade-offs" is Juanita M. Kreps, Secretary of Commerce (Business Week, July 31, 1978). Such backlash is typically undiscriminating--it seeks to reduce the government power indiscriminately, cutting into both its ability to advance the public welfare and to unnecessarily complicate, harass, etc. The best reaction is anticipatory rather than post hoc adaptation: to apply government powers now more parsimoniously and judiciously, before such a backlash rises to a level at which it will seriously undermine the ability to govern.

An excessively liberal use of government power has already led to a regulatory overload. The regulatory overload results in an inability to reinforce the regulations, often not voluntarily complied with, along with the threefold negative outcome of (1) loss of the purposes sought, (2) neglect of more workable alternatives

(because it is assumed that the regulation will work), and (3) increased alienation from regulation and from government (due to inequities that uneven enforcement generates and the contempt for law it breeds).

Second, there seems to be a public overload. The high level of public resentment of government intervention, regulation, "Big Government," is well established. That is, the majority of the public is greatly disaffected and distrusting of most institutions, especially the executive and legislative branches of government. (Alienation, measured systematically since 1966, reached a high point in 1974; it subsided somewhat at the beginning of the Carter administration.) In the area at hand, the public seems to prefer to be provided with information (e.g., about ingredients of products), rather than be told whether or not to consume given products.* Since the labels suggested for alcoholic beverage containers seem to focus on product usage rather than content information, they are likely to be less well received than ingredient labels.

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* For some limited evidence to this effect, see "Nutrition and the American Food System: Part II," presented by Dr. Tim Hammonds for the Food Marketing Institute, Family Circle National Nutrition Conference, June 1-2, 1978, pp. 7-8.

Although lack of research precludes empirically supported conclusions on the subject, informal interviews and observations indicate that the public is overloaded with health warnings. Typical public reactions to the flood of warnings are, "You've got to eat something." "They tell you the water is polluted, the air--full of toxins, the bread has too much iron, the peanuts--fungus. What is one to consume?" The result is a tendency to ignore most, if not all, warnings.*

While the highly educated may be able to discriminate between warnings, most members of the public may well not be in such a position. Even specialists disagree, for instance, on the effects of coffee, low-cholesterol diets, etc. The net effect seems to be a very low level of compliance in most areas. (There are, of course, other reasons for the low compliance, but overload seems an important reason at present, and one gaining in significance.)

The overload may be indirectly reflected in that only 15 percent of groups of women across the U.S.A. (aged 20 to 45, with at least two children living at home, middle to low-middle income and education) felt "strongly" about "eating only what is good for them." Four times more, 60 percent, said they "try for a balanced diet, but don't make

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* This argument was recently advanced on The Wall Street Journal editorial page (August 17, 1978) in reference to toxins in peanuts, also found in many other fruits and vegetables.

a big deal of it." Another 17 percent agreed with the statement that they "eat what they like and don't worry about it"--as opposed to the 15 percent who are greatly concerned with eating only what is good for them.*

Here the application of a system of graduated alerts used in other areas appears called for, for precisely the same reasons. For example, on beaches where red flags are used to signal dangerous waters, the prohibition of public use is often backed up by lifeguards and police if necessary; black flags indicate dangerous waters that might be used only with caution if one is a good swimmer; blue flags generally indicate safe waters (or some other such differentiation). Similarly, New York City has a graduated alert system for water shortage problems. Under the least critical condition, Alert Number 1, police shut off running hydrants and limited hours are set for watering of lawns. In the second phase, Alert Number 2, lawn watering and the flushing of sidewalks are banned. Here, police receive the added assistance of fire personnel in shutting hydrants. In the most critical phase, Alert Number 3-Emergency, police, fire personnel, and the Department of Environmental Protection all assume responsibility to shut running hydrants. Just as different labels may illustrate varying degrees of

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* A Yankelovitch study presented at the Food Marketing Institute, op. cit., p. 3.

seriousness or danger, the same may be indicated by various phases in the mobilization of personnel.

In Los Angeles, three different alerts are employed to denote varying levels of smog pollution problems. During a first-stage health advisory, children, the elderly and those with respiratory and cardiac problems are warned to remain indoors. Industries are asked to voluntarily control pollution-producing activities. For the more serious second-stage health advisory, the general public is warned to refrain from any strenuous activity, industrial emission must be cut by 20 percent, certain activities, such as the unloading of crude oil, are completely curtailed, and there is some mandatory car pooling. The most critical condition is the third-stage health advisory, or smog holiday, where all business and industry is shut down and only authorized vehicles are permitted to operate on the roads.

In each case the logic is the same: High alerts are used sparingly with a graduated alert system assisting the public in differentiating between higher and lower problem conditions.

It seems advisable to apply this approach of graduated response to the area of food, drugs, and beverage alerts. This could take the form of a graduated system based on the level of danger (probability) and the extent of

disutility. The following suggestion, which could be further refined, is used merely to illustrate the point. In outlining it, I tried to draw on existing traditions and symbolism:

(1) A black skull and crossbones: Very high possibility of danger; fatality or severe injury likely to result. (A proper label for concentrated toxins and high-voltage electricity.)

(2) Dark red labels, posters, inserts, etc., with black imprinting: High probability of danger and/or serious injury likely to result. (May be suitable for cigarette packages.)

(3) Pale blue label, any color imprinting, labels, posters, inserts, etc.: Suitable for lower probability and for lower level of injury. (E.g., for solutions for external use whoe ingestion would upset one's stomach.)

(4) One or more public announcements by the proper authorities as the lowest level of alert.

FAS IN A GRADUATED CONTEXT

I suggest that, at this point, FAS may well fall between categories 3 and 4, for the following reasons:

A. The Status of the FAS Data

Needless to say, the status of the relevant data greatly affects the policy posture. While we are not qualified to judge the scientific data on its own merit, on the basis of

scientists' reports it seems proper to refer to it as being partial and uneven. That is, the limitations are not merely those we face with most, if not all, scientific data--that it is not definitive, a continuous process of revising and updating, the very nature of science. Here--major pivotal questions remain quite open, especially (i) the scientists involved indicate that no conclusions have been reached concerning the amounts of alcohol which would pose danger. (ii) It is not known if FAS is related to continuous or just occasional use of alcohol. And (iii) it is not established at what stages of the fetus formation complications related to alcohol intake can occur.

The main finding that seems relatively well established is that continuous heavy drinking is detrimental to the fetus.

B. Policy Implications: Questions of Sub-Populations

As heavy drinkers tend to be addicted and must be expected to be least responsive to label warnings, while more moderate drinkers can be expected to be relatively more responsive--the question of the effect of smaller amounts is critical for the decision of whether to label or not to label, and this is a question for which we have very few answers at this stage.

The status of moderate drinkers is particularly pivotal, first, because most women who drink do so moderately. A study published in 1968 provides the following data:*

* Another source estimates the proportion of heavy drinkers among females to be even smaller, i.e., 4 percent (defined as consuming more than 2.5 oz. of liquor a day). National Clearinghouse for Alcohol Information.

Drinkers, Heavy Drinkers and
Heavy-Escape Drinkers, by Sex and Age*

	Total Sample	Drinkers		Heavy Drinkers[b]	Heavy-Escape Drinkers[b]
	N[a]	%	N	%	%
Women					
Age 21-29	256	70	181	9	6
30-39	345	72	252	9	7
40-49	333	65	218	12-	6
50-59	265	50	132	3	3
60+	367	44	154	2	1
No age given	3			2	

[a]Percentages are based on weighted sample. N = numbers of interviews in each group. Classifications defined in text.

[b]Base: total drinkers.

Second, moderate drinkers are much more likely to respond to "formal" communication and educational efforts than heavier drinkers.

Third, <u>if</u> moderate drinkers must <u>also</u> be reached, there is a much greater justification for labeling than otherwise because then <u>all</u> drinkers must be informed. In contrast, if the message is only for heavy drinkers, there is less reason to try to reach all drinkers.

<u>However</u>, the data on the undesirable effects of <u>moderate</u> drinking on the fetus seem to be very weak. (The best strategy

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* Don Cahalan and Ira H. Cisin, "American Drinking Practices: Summary of Findings from a National Probability Sample," <u>Quarterly Journal of Studies on Alcohol</u>, Vol. 29, No. 1, March 1968, p. 137.

here may turn out to be to encourage people to consume foods before they drink or to drink while eating, rather than urging them to abstain completely.) Until the question of the effects of moderate drinking is clarified, it will be particularly difficult to determine what the labels should state. In short, at present the risk that labels will either underwarn or overwarn is particularly high.

Similarly, if it is established that occasional excessive drinking ("binge" drinking) can also cause FAS, different warnings will have to be issued since the binge drinkers seem to be a third sub-population, distinct from the moderate (or social) drinker and the heavy (or addicted) drinker. Unfortunately, it is not possible at this point to base a policy on data on this issue because present data on binge drinking seem to be very thin.

Finally, the warning may well have to be quite different if the risk period encompasses the first month (or two) of pregnancy, when many women are unaware of their condition, as opposed to later stages. In the former case, all women capable of becoming pregnant, approximately ages 14 to 50, would have to be advised, while in the latter case it might suffice if a much smaller population, only women who are pregnant, are involved.

Until these issues are clarified further through additional research, at most a warning which is aimed at heavier drinking seems justified. To target a high-powered alert at

others could backfire if it is later established that moderate drinking, or drinking early in pregnancy, are not harmful. Indeed, under these circumstances, the federal government might be sued for damages caused to those who lost the benefits moderate drinking is reported to provide.

At the same time, on the basis of the consumer/public right to know, whatever information is available should not be withheld from any group. Hence, whatever data there are on the effects of any kind of alcohol consumption in any group should be released and perhaps posted, but there seems insufficient justification at this stage for extensive efforts. Most heavy drinkers are very unlikely to respond to labels; others--may not be at risk, or best approached differently.

C. Policy Implications: Questions of Legitimacy

The stronger the data, the better the defense one can pose against criticism, and the easier it will be to legitimate the required warnings. Of course, no scientific data is ever definitive and the critics will not be silenced merely by stronger data. Nevertheless, the stronger the data, the less vulnerable a policy, at least in the eyes of the main science community and the responsible media.

Also, scientific data go through a sociological process in which they are publicly debated and a slow consensus emerges on the status of the data. This process is quite different from scientific evaluations, internal to the scientific

community. The public dialogue serves to convince the public of the legitimacy and implications of the new findings. (The public seems to be vaguely aware that not all initial findings will hold in the longer run or have the same power, and it takes the kind of repetition public debates generate to get the message across.) Thus, the fact that a group of Harvard experts redefined death as a flat brain wave curve for forty-eight hours did not reach most Americans, but following the public debate around the Quinlan case, an estimated 30 percent of the public (a very high figure) changed their view about when a person should be considered dead. Another example of data which are considerably well processed is that concerning the relative demerits of heroin vs. marijuana (once lumped togetner as illicit drugs). In contrast, data about FAS are not widely known, or their implications discussed. Hence, the legitimacy of the claim that alcohol will damage a fetus is not at all well publicized. Regulation would more likely be respected if the data were first "processed" more publicly. (The preceding statements may be surprising in view of the repeated public hearings and press stories on FAS. But experience suggests that such information spreads very slowly and Washington-based civil servants tend to vastly overestimate the public "visibility" of acts such as media exposure. I would estimate that no more than 20 percent of the public know about FAS and less than 10 percent are able to properly characterize what it means.)

The fact that FAS data at this stage are poorly processed suggests that the time is not ripe for relatively tough measures from this viewpoint. If higher levels of alert were desired on other grounds, e.g., if new data suggested frequent FAS risk at early stages of pregnancy, then the public dialogue could be intensified. One of the most effective ways of doing this would be to foster some drastic measures (for instance, sending a registered letter from state health departments to all women aged 14 to 50, or at least to pregnant women, warning that alcohol may harm their fetus).

Finally, legitimacy--the public sense that the government is acting judiciously rather than arbitrarily--is affected by many factors over which any specific government agency has little or no control. There are, however, a few matters which interagency coordination, and specific agency efforts, do affect. Among these is the placement of matters into proper contexts. Hence, I strongly recommend that warnings regarding FAS be reviewed together with other warnings issued by the Office of Tobacco, Alcohol and Firearms, as well as by other bureaus and agencies (if such interagency review is practical). Otherwise, one should expect adverse public reaction to inconsistencies such as extending a warning on FAS, but not on guns and automobiles* and children's tricycles (which are designed

* It might be said that people know about the dangers of automobiles, and hence they do not need to be labeled. We suggest that very few know, for instance, that in various safety designs, e.g., of bumpers, cars are built to be safe at 30 miles per hour, but not at higher speeds.

with a tendency to fall backwards). The FAS may be singled out because of the novelty of the findings, great moral and emotional status of harming yet-unborn children, interagency status/jurisdiction problems, and the relatively lesser clout of the liquor industry as compared to, say, gun and maybe auto lobbies. However, these are not reasons the public will consider as sources of legitimacy. Although the following commentary sent to BATF is by an interested party, it may well seem quite justified to many Americans who do not have a special stake in the industry:

> I can hardly believe that you intend to label wine with a warning to pregnant women about alcohol consumption! Do manufacturers of cookies and candy warn diabetics of the dangerous sugar content of these products? Do pretzel packages indicate a potential danger to people on salf-free diets? Are food items heavy in saturated fats and cholesterol labeled thus for persons with heart and vascular problems?*

Some generic guidelines may arise out of such inter- or intra-agency review, and would provide a rationale as to what level of danger and "size" of potential harm call for what kind of alert. (The Consumer Commission has developed such a scale. In the same vein, the Occupational Hazard Safety Act recently decided to focus on major rather than technical abuses).

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* Meredith Ann Edwards, Mantanzos Creek Winery, Santa Rosa, California, March 14, 1978.

D. Conditions for Effectiveness of Labels and Other Modes of Public Warning

Another consideration relevant to determining what level of alert to issue, and it does not favor a high-level one in the case of FAS, is how effective such warnings can be expected to be. One condition is substitutability. Reference is not to the widely-known economic idea but to a psychic one. The question focuses on whether there are easy ("near") substitutes available to a banned or otherwise "warned against" product, of similar attributes and costs. This seems not to be the case for alcohol. It is hence informative that, while "the impact of the warning label alone [on cigarettes] was difficult to assess," a scientific euphemism for no effect was found, and "although the total number of cigarettes consumed had not decreased, smokers had switched from non-filter to filter cigarettes."*

People seem to have a need, at least in our kind of society, and most others, for some tension-management. Certain drugs, foods, and liquor are used throughout the world to achieve such relaxation. To inform all women from ages 14 to 50 (or all pregnant ones) that they should cease consuming alcohol (especially if moderate and binge drinking are found to be harmful), and expect them to heed the warning, does not speak to their tension-management need.

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* Donald Kennedy, Hearing before the Subcommittee on Alcoholism and Drug Abuse, U.S. Senate, January 31, 1978, p. 95.

The warning would be vastly more effective if it turned out that drinking wine or beer has no harmful effects on the fetus (a rather unlikely possibility), so that women could be advised to switch to these from hard liquor, or--if it turned out that women could be told to eat before they drink (to dilute the effects of alcohol). We expect warnings to be less effective the fewer "near" substitutes are available. Many people seem to have switched from liquid protein diets to other diets; from high to lower tar cigarettes; from birth control pills to other contraceptives; much less effective--to call for total abstinence from cigarettes, sex, or reduce their caloric intake.

Other conditions which will affect the effectiveness of labels (and other "formal," i.e., printed, broadcasted, means of communication) include whether the product is addictive or not (while one can develop an addiction to any product,* say even ice cream, some products seem much more addictive than others); whether information is anxiety-provoking or "positive," etc. Hence, positive experience with ingredient labels, which consumers use to select items with certain attributes rather than others, does not automatically apply to warnings against alcohol. Here, not only might substitutability be much lower (akin to the low level for avoiding cigarettes), but addiction may be high, and anxiety (about

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* B. Barber, Drugs and Society (New York: Russell Sage Foundation, 1967).

one's child) high. High anxiety seems to generate avoidance and repression of information rather than high compliance. This point is illustrated in that, of 417 reasons given for reading labels on over-the-counter drugs, only 15 (3.6 percent) concerned "warning" or "side effects," 48 (11.5 percent) "to avoid harm," while 115 (27.6 percent) read the label for ingredients/strength. (Other reasons given are difficult to classify.)*

While it is true that labels seem less effective when they concern high anxiety items, this is not to suggests (as several others have implied)** that the information should be withheld so as not to generate more anxiety. Women are not to be treated as neurotic, infantile creatures who need to be protected from tension. On moral grounds, it would be unethical to prevent millions of pregnant women from making an informed choice on the implausible idea that this bit of anxiety, in a world riddled with anxiety, would be the one that would tax their tolerance to the breaking point.

Finally, it is methodologically unsophisticated to rely on what consumers say they have found useful for evidence on

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* Gary E. Blanken, Consumer Attitudes Toward Over-The-Counter Drug Labels, Office of Planning and Evaluation, FDA. February 1976, No. 28, Table 7. For additional data and discussion, see Consumer Nutrition Knowledge Survey Report I, 1973-74, U.S. DHEW FDA. Publication No. 76-2058, 1974 and Report II, Publication No. 76-2057, 1976.

** Letters to BATF: (1) C. Frederic Shroeder, president, Finger Lakes Wine Growers Association, March 13, 1978; (2) Joyce Lemons, Honeywood Wines of Oregon, Feb. 27, 1978; (3) Comments submitted by the Distilled Spirits Council of the U.S., 1978.

the usefulness of labels.* And of course the fact that 45 percent said they stopped using a product because they read or heard it was unsafe** may not mean that they continued to avoid it. On the contrary, "washout" studies suggest that many, if not most, will return to traditional usage. Hence, behavioral studies, including at least a two-year follow-up, would be more impressive.

E. Potential to Cause Harm

Unfortunately, not all government policies, even when formulated with the best of intentions, contribute to the public well-being. An example of federal labeling which on balance may cause more harm than good is the U.S. grading of meat. Department of Agriculture studies suggest that many consumers do not understand the terminology.*** (The U.S. Agriculture Department recently widened the "choice" category to include the upper third of meat formerly graded as "good." Most consumers seem unaware of the change and many are unable to make sense of the term "choice.") More important, a wide

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* Cf. statement by Donald Kennedy, Commissioner, Food and Drug Administration, before Subcommittee on Alcoholism and Drug Abuse, Committee on Human Resources, U.S. Senate, January 31, 1978, pp. 8-9.

** Ibid., p. 10.

*** T. Q. Hutchinson, Consumers' Knowledge and Use of Government Grades for Selected Food Items, U.S. Dept. of Agriculture, Economic Research Service, Marketing Research Report No. 876. April 1970.

system of abuse has developed in misgrading beef, which inflates the costs to the consumers, relying on what seems to them federally bonded grades.

Public policy makers should subscribe to the original Hippocratic Oath of at least not causing harm. In the case at hand, this might take place if the government would require certain kinds of labels on liquor bottles, e.g., ones which list also reported benefits of drinking* (which were cited in a number of letters),** or--list only harmful effects without dissociating itself from the product. By and large, a government label, even before it is read or if it is not read at all, seems to imply authoritative approval to some people. From this viewpoint, of special interest is a study of nutrition labels reported by Paul Fine Associates:

> Our study indicates that the effect, to the extent there will be any, would be that of providing a Federal stamp of approval to foods carrying the required labelling--a "stamp" synthetic food manufacturers could easily obtain, but which natural foods could not easily obtain. This is because it is easy to spray cereal flakes with precise amounts of required nutrients,

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* Dr. Arthur L. Klatsky, director of the coronary care unit at Kaiser-Permanente Medical Center in Oakland, California, is cited as stating that moderate alcohol drinking reduces probability of coronary by 30 percent. His conclusion is based on a study of 87,000 patients. (New York Times, June 21, 1978)

** Letters to BATF: (1) C. Frederic Shroeder, President, Finger Lakes Wine Growers Association, March 13, 1978; (2) Report submitted by the Distilled Spirits Council of the U.S., Inc., 1978; (3) Valerie E. Ahlgren, Ahlgren Vineyard, Boulder Creek, California, March 10, 1978; (4) Scott Setrakian, California Growers Winery, Inc., March 16, 1978.

> but fruits and vegetables--which do not grow in terms of RDA's--cannot be "fortified" nor can one be precise about their amounts of RDAs. Since the rules would specifically deny any special claims of the superiority of natural foods over synthetic ones--and since the public now believes that "real" fruits, vegetables, and cereal grains are better than synthetic ones--the effect would be to say to those consumers who have been worried about synthetic foods that they need not worry so long as the products have the proper label. The rule also says to the public that "natural" food is not better food.*

A federal label on alcohol may well imply more approval of consuming it (at least by persons not pregnant) than is in the public interest. At least, the "costs" of such federal legitimization of liquor should be weighed against the benefits of such labels.

F. Economic Costs

Economic costs of regulation are not discussed here. While this is generally an important issue, especially when major industries are threatened or regulation causes increased production costs, this seems not to be a significant issue here.

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* Paul Fine Associates, Oakland, California, letter to the Bureau of Alcohol, Tobacco and Firearms, March 14, 1978.

THE SPECIFICS OF THE ALERT

The preceding analysis suggests that a low-level rather than high-level alert is desired. It does not prescribe precisely what form it should take. It suggests that a high-level alert is not justified because of the sociological status of the data and the problem of overload and the existence of other--more alarming--causes; it suggests that it seems unethical not to alert the public at all; but it does not specify whether posters, labels, public education or what are called for.

In fashioning the specifics of a low-level alert, the following additional considerations come into play:

(1) Several comments submitted to BATF by representatives of the industry suggest that the matter be left to physicians, other health professions, and the women themselves. The Christian Brothers, operators of the Mont La Salle Vineyards, Napa, California (March 17, 1978) noted in a communication to BATF:

> Pregnant women should seek medical advice from a physician or clinic. They also have available to them many books and pamphlets. Generally, too, they have learned something of physiology, nutrition and hygiene while in school.

Joyce Lemons of Honeywood Wines in Oregon (February 29, 1978 letter to BATF) reflected the sentiments of many on this matter:

> The only safe, sane source for accurate, comprehensive information on drinking and pregnancy is a medical or health professional, not the label of bottle.

The extent to which one can rely on such professional care depends in part on the specifics of the FAS data. This reliance would be impossible if early and moderate drinking have an effect, because then all women in fertile ages must be notified (and all persons--if the proper social climate is to evolve.)* Many of these will not be in professional care before pregnancy. Even if only heavy and later-in-pregnancy drinking are detrimental, one cannot ignore those women who seek little or no prenatal care.

Furthermore, relying on physicians to transmit the information to women (or to pregnant women) is very unadvisable in view of the poor record of physicians in transmitting such "preventive" information, as the experience with birth control pills suggests. (In 1972, neither Barbara Seaman nor I could find a single woman who received the information from her physician.)**

Requiring posters in liquor stores, and in other stores in those states in which liquor is sold in other shops, placed in the appropriate section, as well as posters in prenatal

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* For discussion of this point, see below.

** See Barbara Seaman, Free and Female (New York: Coward, McCann & Geoghegan, 1972), p. 232, and Amitai Etzioni, Genetic Fix (New York: MacMillan Publishing Co., 1973), p. 167.

care clinics, seems a low-cost, relatively easy-to-update medium. Labels on millions of bottles are harder to update and probably more costly.

Also, such posters are less likely to have a legitimating effect on liquor consumption since they are not directly linked with the product, but serve to call attention to a specific feature rather than provide a full assessment of the product's merits and demerits.

The information about FAS should be integrated into other public education and preventive health information programs of the kind which encourage people to maintain proper weight and diet, but large efforts or expenditures to achieve this seem undesirable both because of the state of the FAS data, and because such programs tend to have a very limited effectiveness.*

Adding one penny (or more) to the tax on alcohol, with the revenue specifically designated for public education programs on the various effects of alcohol, could go a long way to provide the needed back-up for a more intensive preventive effort.

One of the most interesting suggestions in the body of commentary we reviewed was to use funds generated in this way

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* For additional discussion, see Amitai Etzioni, "Individual Will and Social Conditions: Toward an Effective Health Maintenance Policy," The Annals of the American Academy of Political and Social Science, Vol. 437 (May 1978), pp. 62-73.

to finance treatment facilities for alcoholics. There is a need for more such facilities and it is proper for the industry which profits from the sale and promotion of consumption of alcohol, and the consumers who use it, to help fund such facilities. Pregnant alcoholics, alerted by the new information, may find here a place to turn. This is especially important if only heavy drinking is found to be detrimental. Most heavy drinkers cannot break the habit by themselves but many do have a measure of motivation to stop. This motivation may get a boost once they find themselves pregnant, but they still need help in overcoming their habit.

Also, public service announcements on television and radio may do more good than labels, although if one could have all the aforementioned and labels, they might benefit from the interaction effect. The trouble with labels is that they are basically informative, cognitive. The industry would not allow a truly persuasive emotive appeal on the labels. Public service announcements can be made to appeal more to motives, sentiments, and values, quite necessary in addition to, not instead of, informing, if people are to change their minds.*

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* See, for instance, Martin Fishbein on three levels of consciousness, "Consumer Beliefs and Behavior With Respect to Cigarette Smoking: A Critical Analysis of the Public Literature," Report Prepared for the Federal Trade Commission, May 1977, p. 4.

Finally, special attention should be paid to the social climate of drinking as distinct from the act itself. Recent studies of cigarette advertisements suggest that their effect, above and beyond prompting people to switch brands, changes the social image of the smoker, making it socially more acceptable, for instance, for women to smoke.* Once this is achieved, smoking will be promoted by the "normal" social field itself. Similarly, data indicate that it is becoming more acceptable for women to drink.

> However, attitudes toward drinking by women and girls have changed in recent years. In a 1974 survey on teenage drinking sponsored by the National Institute on Alcohol Abuse and Alcoholism (Rachael et. al., 1975) only 28 percent of the 13,000 teenagers surveyed agreed with the statement, "It is worse for a girl to drink than for a boy." Not only have attitudes toward girls drinking relaxed somewhat, but girls' drinking behavior is changing as well. While drinking has increased among both boys and girls in recent years, it has increased more rapidly among girls (U.S. Department of Health, Education, and Welfare, 1974). In the 1974 teenage survey 87 percent of senior girls reported having had a drink of alcohol at least once.

A similar development was noted by Edith S. Gomberg:

> How clear are the rules about women's social drinking in American society and how do the rules, particularly the sanctions relating to drinking,

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* Sharon C. Wilsnack, "The Impact of Sex Roles and Women's Alcohol Use and Abuse," Alcoholism Problems in Women and Children (eds.) Milton Greenblatt and Marc A. Shuckit (New York: Grune and Stratton, 1976), p. 57.

> relate to sexual roles? What we can say with certainty is that the drift of change since World War I has been in the direction of more permissiveness. One evidence of this is in the advertising material used by liquor companies, a reflection of changing mores. As with cigarette advertisements, the first "breakthrough" was the mere presence of a woman while the man was drinking, and the second was having glasses clearly intended for both or even in their hands. Recently, for the first time, women have begun to appear in liquor advertising on their own, one company advertising Scotch and the single girl.*

Younger women drink more than older ones ("only 25 percent of those 21-29 said they had never drunk, compared to 46 percent of those 60 or older"),** and more than previous generations.***

> In March 1958, ...45 percent of the women, were drinkers; in May 1960, ...54 percent; in February 1964, ...women 56 percent; in February 1966, ...women 61 percent. Data courtesy of the American Institute of Public Opinion (Gallup Poll), Princeton, N.J. The Gallup question was: "Do you ever have occasion to use alcoholic beverages such as liquor, wine, or beer, or are you a total abstainer?"

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* Edith S. Gomberg, "Alcoholism in Women," The Biology of Alcoholism (ed.) Benjamin Kissin and Henri Begleiter (New York: Plenum Press, 1976), p. 125.

** Ibid., p. 144.

*** Don Cahalan and Ira H. Cisin, "American Drinking Practices: Summary of Findings from a National Probability Sample," Quarterly Journal of Studies on Alcohol, Vol. 29, No. 1, March 1968, p. 144.

If it is considered beneficial for pregnant women, their future children, and the public (which bears a good part of the resulting costs if the warning is ignored) not to consume alcohol, it will not be enough to merely inform women. It will also be necessary to help create a social climate which recognizes that it is unbecoming for a pregnant woman to drink. Thus, just as public service announcements try to break the idea that it is socially well-mannered to offer the driver "one more for the road," it will be necessary to establish that it is asocial to offer a drink to a pregnant woman. Public service announcements and public educational campaigns, combined with the advice of physicians and other health professionals, are likely to be relatively more effective than labels or posters in bringing about this change in the social climate, although both of these might help.

A specific point in time should be set, say two years hence, at which new data regarding FAS and public use of health warnings will be reviewed, possibly calling for higher levels and investment in public health alerts in this area. In any event, a systematic approach rather than case-by-case seems badly needed.

LIMITATIONS OF THIS COMMENTARY

The preceding discussion is based on a layman's understanding of the scientific data involved; on a social scientist's application of existing social science knowledge, which is inherently limited, especially when not backed up by a

study directly tied to the issue at hand. No systematic review of the research on the effect of labels was attempted here because the data is very thin, and much of it is unavailable because it was collected by private companies which refused to release it. And, whatever data are available apply to the condition at hand almost exclusively by way of analogue rather than dealing directly with health warnings to pregnant women. It also should be noted that part of the issues involved entail value judgments, especially on the public's right to know.

This memorandum was prepared at the request of the Research and Regulations Branch at the Bureau of Alcohol, Tobacco and Firearms of the U.S. Treasury. The views expressed here are solely those of the author. No consumer groups or relevant industries communicated with the author, nor were they consulted in preparing this memorandum. Their written comments (submitted to the Bureau of Alcohol, Tobacco and Firearms, U.S. Treasury) were studied but not used as a factual data base.